FORMULATION DEVELOPMENT AND EVALUATION OF IBUPROFEN LYSINE IMMEDIATE RELEASE TABLETS BY DIRECT COMPRESSION METHOD

Dissertation submitted in partial fulfillment of the requirement for the award of the Degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

By

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LIST OF ABBREVIATIONS USED

API	-	Active pharmaceutical ingredient
AR	-	Analytical grade
BP	-	British Pharmacopoeia
°C	-	Degree Celsius
Conc.	-	Concentration
DEC	-	Drug Excipients Compatibility
CRC	-	Child resistant closure
g	-	gram
EP	-	European Pharmacopoeia
F	-	Formulation
F1	-	Dis -similarity factor
F2	-	Similarity factor
HPLC	-	High Performance Liquid Chromatography
ICH	-	International Conference on Harmonization
IR	-	Immediate release
JP	-	Japanese Pharmacopoeia
mg	-	Milligram
mL	-	Millilitre
mM	-	Millimole
mins	-	Minutes
ND	-	Not detectable
NLT	-	Not less than
NMT	-	Not more than

NSAID's	-	Non steroidal anti-inflammatory drugs.
P^H	-	Negative logarithm of hydrogen ion
q.s.	-	Quantity sufficient
RH	-	Relative Humidity
RLD	-	Reference Listed drug
Rpm	-	Revolutions per minute
USP	-	United States Pharmacopoeia
Wt	-	Weight
w/w	-	Weight by Weight
w/v	-	Weight by Volume

1. INTRODUCTION

1.1 ORAL DRUG DELIVERY SYSTEMS

Streubel et al., **(2010**) reported oral drug delivery has been known for decades as the most widely utilized administered route among all the routes that have been employed for dosage forms. The reasons that the oral route achieved such popularity due to it is safety, convenience, it does not need assistance, non invasive, often painless, the medicament need not be sterile and also is cheaper. Both solid dosage form as well as liquid dosage form given orally. The various dosage forms administered orally, the tablet is one of the most preferred dosage forms because of its ease of manufacturing, convenience in administration, accurate dosing, stability compared with oral liquids and because it is more tamperproof than capsules

1.2 Immediate release dosage form

Rajpoot et al., **(2011)** develop the immediate release solid oral dosage forms are classified as either having rapid or slow dissolution rates. Immediate release dosage forms are those for which ≥85% of labeled amount dissolves within 30 min. For immediate release tablets, the only barrier to drug release is simple disintegration or erosion stage, which is generally accomplished in less than one hour.

Oral route of drug administration is perhaps the most appealing route for the delivery of drugs. Of the various dosage forms administered orally, the tablet is one of the most preferred dosage forms. The bioavailability of drug is dependent on in vivo disintegration, dissolution, and various physiological factors.

The gastrointestinal tract provides sufficient fluid to facilitate disintegration of the dosage form and dissolution of the drug. The large surface area of gastric mucosa favors the drug absorption. Therefore, the oral route has continued to be the most appealing route for drug delivery despite the advancements made in the new drug delivery systems. Banker and Anderson stated that at least 90% of all drugs used to produce systemic effect are administered orally.

Immediate release tablets have received much attention in recent years, as they are preferred by pediatrics and geriatric patients. Bioavailability of a drug depends in absorption of the drug, which is affected by solubility of the drug in gastrointestinal fluid and permeability of the drug across gastrointestinal membrane. The drugs solubility mainly depends on physical & chemical characteristics of the drug. However, the rate of drug dissolution is greatly influenced by disintegration of the tablet.

The disintegration test is an official test and hence a batch of tablet must meet the stated requirements of disintegration. Disintegrants, an important excipients of the tablet formulation, are always added to tablet to induce breakup of tablet when it comes in contact with aqueous fluid and this process of desegregation of constituent particles before the drug dissolution occurs, is known as disintegration process and excipients which induce this process are known as disintegrants.

The objectives behind addition of disintegrants are to increase surface area of the tablet fragments and to overcome cohesive forces that keep particles together in a tablet.

Ansel et al., (**1999**) An ideal dosage regimen in the drug therapy of any disease is the one, which immediately attains the desired therapeutic concentration of drug in plasma (or at the site of action) and maintains it constant for the entire duration treatment. This is possible through administration of conventional

dosage form in particular dose and at a particular frequency. Thus drug may be administered by variety of routes in a variety of dosage form.

Martin et al., (**2003**) Drugs are more frequently taken by oral administration. Although a few drugs taken are intended to be dissolved with in the mouth, the vast majority of drugs taken are swallowed. Compared with alternate routes the oral route of drug administration is the most popular and has been successfully used for the conventional delivery of drug. It is most natural, uncomplicated, convenient, safe means of administering drugs, greater flexibility in dosage form design, ease of production and low cost

1.3.TABLET

Gabrielsson et al., (**2002**) reported current market, tablet is most widely used dosage form because of ease of administration and convenient for industry to manufacturer. In pharmaceutical industries, manufacturing of tablets are usually focused on the optimization of the excipients mixture composition to obtain a product that meet established standard.

Parmar (**2009**)The tablet dosage form is a versatile drug delivery system. Different types of tablet formulations are available, which could be broadly classified based on: (1) route of administration such as tablets for oral delivery, sublingual delivery, buccal delivery, rectal delivery or vaginal delivery, and (2) formulation characteristics such as immediate release tablets, effervescent tablets, melt- in-mouth or fast dissolving tablets, delayed release or extended release tablets. In all the cases, the general manufacturing process, machinery used for preparation of tablets and materials used are similar.

1.4 DIRECT COMPRESSION:

Rane et al., (**2009**) Direct compression has taken the centre stage in tablet manufacturing because the process avoids many of the problems associated with granulation methods. It is a simple, economical process and because heat or moisture is not required, it is suitable for unstable compounds. However, the success of the direct compression process is determined to a greater degree by the excipients chosen because they impart flow and compression characteristics to the powder blend.

Buwalda et al., (**1997**) Starch is a versatile, cheap and readily available as found wide application in tableting as a binder, disintegrant, diluent, lubricant and glidant. The native form of starch possesses poor flow and compression properties making it unsuitable for direct compression. researchers have made attempts to improve on the flowability and compressibility of starch by modification in order to make it adaptable for direct compression. -

NON STEROIDAL ANTI-INFLAMMATORY DRUGS

Non-steroidal inflammatory drugs usually abbreviated toNSAIDs these are a class of drugs that provide analgesic and antipyretic effects and in higher doses it produces anti-inflammatory effect. The term “non-steroidal” distinguishes these drugs from steroids

CLASSIFICATION:

NSAID's can be classified based on their chemical structure or mechanism of action older NSAIDs were known long before their mechanism of action was elucidated and were for this reason classified by chemical structure or origin newer substances are more often classified by mechanism of action.

1) SALICYLATES

1) Aspirin (acetyl salicyclic acid)

2) Diflunisal

3) Salsalate

2) PROPIONIC ACID DERIVATIVES:

1) Ibuprofen

2) Dexibufrofen

3) Naproxen

3) Fenoprofen

4) Ketoprofen

5) Dexketoprofen

6) Flurbiprofen

7) Loxoprofen

3) Acitic acid derivatives

1) Indomethacin

2) Sulidac

3) Ketrolac

4) Diclofenac

4) Enolic acid (Oxicam)derivatives

1) Piroxicam

2) Meloxicam

3) Droxicam

5) Fenamic acid derivatives (Fenamates)

1) Mefanamic acid

2) Meclofenamic acid

3) Flufenamic acid

4) Tolfenamic acid

6) Selective cox-2 inhibitors, Coxibs):

1) Celecoxib(FDA alert)

2) Rofecoxib

3) Valdecoxib

4) Parecoxib

5) Firocoxib

7) Sulphanilamides

1) Nimesulide

8) Others

1) licofelone

2) Lysine clonixinate

9)Naturals:

1) Hyperforin

2) Figwort

LITERATURE REVIEW

Martin et al., (**1990**)investigated lysine salt of *d,l*-2-(4-isobutylphenyI)-propionic acid (ibuprofen lysine) was administered as a single oral dose of 500 mg by means of commercially available coated tablets Drug tolerability was excellent for the oral administration of ibuprofen lysine as well as for the intravenous treatments with ibuprofen free acid. Only mild and transient adverse drug reactions such as mild burning or dragging sensation during injection or mild redness at the site of injection were reported.

Tadeuswz et al., (**1993**) studied lack of significant differences between the AUC values from suppository and the intravenous studies with similar doses implies complete absorption of ibuprofen from all the suppositories Ibuprofen lysinate was absorbed significantly more readily than the free acid from suppositories. The lysinate suppository with a lipophilic surfactant had a higher absorption rate constant than that with a hydrophilic surfactant. The k_a values did not significantly differ for a twofold difference in dose. Equations were developed to calculate true AUC and area under the moment curve (AUMC) values when A exceeds B, and to transform C versus t plots to the origin with A' = A = B.

Donald et al., **(1995**) reported single-dose, double-blind, parallelgroup, single-site study compared ibuprofen lysine 400 mg with acetaminophen 1000 mg and placebo in 240 patients with moderate-to-severe postoperative dental pain. The relative onset of analgesic response, overall analgesic efficacy, duration of effect, and safety were assessed over a 6-hour postdose period. Analgesic efficacy was assessed by patient self-rating of pain intensity, pain relief, time to meaningful pain relief, need for additional analgesic medication, and patient global evaluation. Ibuprofen lysine had a significantly faster onset of action with greater peak and overall analgesic effect than did acetaminophen.

Inken Stoye (**1998**) studied a contribution to the investigation of molecular association of phospholipids and amphiphilic substances like, e.g. non-steroidal anti-inflammatory drugs. Our research focussed on physico-chemical characterization of ternary systems containing ibuprofen lysinate, lecithin and water. The influence of the resulting microstructures on drug release and permeation through excised human stratum corneum was also investigated.. A special emphasis was laid upon the storage-induced transformation of liposomal dispersions into mixed micellar solutions and its influence on drug release and permeation. A model for the transformation process is presented Because of the association of ibuprofen lysinate molecules with phospholipid molecules within the liposomal and the mixed micellar system the share of free ibuprofen lysinate monomers, which can pass through the dialysis membrane in the release experiment, is markedly reduced.

Glowka (**2000**) Studies were performed on the effect of ibuprofen racemate ionization extent on the pharmacokinetics of its enantiomers following administration in suppositories to rabbits. The suppositories, containing 146.3 mg ibuprofen in acidic form (IBP) or 250 mg ibuprofen lysinate (IBPL), equivalent to the above IBP dose, were prepared using lipophilic Witepsol H-15 as a base and administered to rabbits in a crossover design. Compared with IBP, administration of IBPL was followed by faster absorption and elimination of *R* and *S* enantiomers. However, significant differences at $\alpha = 0.05$ were observed only at the stage of elimination. AUC was markedly higher following administration of suppositories containing IBP than following suppositories with IBPL and this pertained to both *R* and *S* enantiomers..

Jörn Lötsch et al., (**2001**) investigated the pharmacokinetic equivalence of two different formulations of ibuprofen lysinate with special focus on the expected effects.Ibuprofen is one of the most frequently used over-the-counter analgesics. Most commercial formulations come in tablets of 200 mg racemic

ibuprofen. This contrasts with several reports that a dose of 400 mg racemic ibuprofen is probably more appropriate to produce the desired analgesic effects . It is therefore reasonable to develop ibuprofen formulations with tablet doses of 400 mg. The present study was designed to compare the stereoselective pharmacokinetics of such a newly developed 400 mg tablet formulation with those of a standard formulation of 200 mg tablets.

Matthias et al., (**2005**) studied bioequivalence between a 400-mg ibuprofen extrudate and lysinate formulation, and to evaluate the relative bioavailability of the extrudate tablet compared to a regular ibuprofen tablet, based on C_{max} and $AUC_{0-\infty}$.. The rate of absorption at fasted state was considerably faster following administration of the ibuprofen extrudate and the ibuprofen lysinate tablet than for regular ibuprofen. However, the overall extent of absorption was not different, and a food effect could be demonstrated for all 3 formulations.

Jacob et al., (**2007**) Patent ductus arteriosus (PDA) is the failure of the ductus that arises from the distal dorsal aortic arch to close during the first few days of life. The treatment options for PDA include “watchful waiting,” pharmacologic therapy with cyclooxygenase (COX) inhibitors (COX-1 and COX-2), such as indomethacin or intravenous (IV) ibuprofen lysine, and surgery when medical interventions have proved ineffective. The clinical trials evaluating the utilization of IV ibuprofen lysine focus on either preventing the persistence of a PDA or treating the PDA in premature infants in whom the ductus does not close within 48 hours of birth. Although the role of COX inhibitors in prophylaxis of PDA has been studied, it has not been clearly delineated. Treatment of PDA in preterm low birth weight infants from the second day of life on with IV ibuprofen lysine has been studied in 4 major and 3 smaller clinical trials. Overall, in 7 studies with 492 patients, the closure rate of PDA was 75.1% with IV ibuprofen lysine compared to 73.5% with

indomethacin. In addition, neonates treated with IV ibuprofen lysine had significantly better creatinine clearance, urine output, serum creatinine, and blood urea nitrogen (BUN) profiles than indomethacin-treated patients. Overall, IV ibuprofen lysine is as effective as indomethacin for closure of PDA, yet is associated with a better safety profile with fewer negative side effects when compared to indomethacin.

Pai et al., (**2008**) Approximately 70-80% of newborns less than 28 weeks' gestational age require pharmacologic and/or surgical intervention to close a hemodynamically significant patent ductus arteriosus (PDA). Indomethacin has been the pharmacologic treatment of choice and has also been used prophylactically in very premature neonates to prevent PDA. The drug, however, is associated with renal and gastrointestinal adverse effects. In July 2006, intravenous ibuprofen lysine became available in the United States for treatment of hemodynamically significant PDA. The mechanism of action for both indomethacin and ibuprofen lysine is through inhibition of prostaglandin synthesis, resulting in ductal constriction. Both drugs appear to be equally efficacious in closing echocardiographically confirmed PDA. Ibuprofen lysine has demonstrated significantly less effects on cerebral, renal, and mesenteric blood flow in premature neonates when compared with indomethacin. A transient but significant increase in serum creatinine concentration, decrease in urine output, and increase in frequency of oliguria were observed with indomethacin when compared with ibuprofen lysine. However, the rate of reopening of the ductus after pharmacologic closure and the need for rescue therapy were not different between the two drugs. In addition, no differences were noted in other outcomes such as frequency of intraventricular hemorrhage, necrotizing enterocolitis, or chronic lung disease, as well as in duration of mechanical ventilation and length of hospital stay. When administered prophylactically, ibuprofen lysine did not prevent intraventricular hemorrhage

nor provide any neurodevelopmental benefits. In addition, ibuprofen lysine has not been adequately studied in neonates of 27 weeks' gestational age or younger. Ibuprofen lysine is as efficacious as indomethacin in treating hemodynamically significant PDA in neonates greater than 27 weeks' gestational age.

Holt et al., (**2008)** To study the physical compatibility of ibuprofen lysine injection (NeoProfen, Ovation Pharmaceuticals Inc., Deerfield, IL) with medications commonly used in the premature neonatal population during simulated Y-site administration. Commonly used intravenous medications in preterm infants were evaluated for physical compatibility with ibuprofen lysine injection. A 20-mL sample of ibuprofen lysine drug product solution was mixed with a 20-mL sample of each of the 34 medications at concentrations used clinically. The mixtures were stored at room temperature and each sample was evaluated for turbidity and physical appearance at time 0 (immediately after preparation) and at 4 hours after preparation.

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Ambat et al., (**2008**) studied the influence of IBU on B–A binding was measured by saturation index and horseradish peroxidase assays. B–A solutions were prepared at B:A ratios of 0.5, 1.0, 1.5 and 2.0 and bilirubin concentrations

of 5 and 10 mg per 100 ml. Drug concentrations used were 142.5, 200 and 285 mg l^{-1} for IBU and 100 and 200 mg l^{-1} for acetyl salicylic acid (ASA). Similar tests were performed on premature newborn sera with bilirubin concentrations of 5 to 10 mg per 100 ml.Displacement of bilirubin was demonstrated only at high IBU concentration and high B:A ratio. However, free bilirubin levels were not shown to increase with increasing IBU concentration

Sheffield et al., ((**2009**) Ibuprofen might have advantages over indomethacin, when used to effectuate closure of a neonate's patent ductus arteriosus (PDA). Several previous studies indicate that platelet plug formation is impaired after administration of indomethacin, On the basis of our present studies, we speculate that ibuprofen lysine administration to neonates with a PDA, when used according to the manufacturer's recommendations, has little adverse effect on platelet plug formation. This information might be a factor to consider when deciding whether to select indomethacin or ibuprofen for PDA closure.

Luke et al., (**2012**) reported Prostaglandins are utilized to maintain the patency of the ductus arteriosus until surgical ligation is performed. When surgical ligation is not indicated, prostaglandin inhibitors. Ibuprofen was initially thought to have less adverse effects, such as a decreased incidence of oliguria, gastrointestinal (GI) toxicity, and cerebral hypoperfusion. The use of ibuprofen has been shown to increase the incidence of pulmonary hypertension.

Patrizia Santi et al., (**2003**) studied in vitro the post-iontophoresis transport of ibuprofen lysine across rabbit ear skin, from ibuprofen lysine water solutions. The results showed a significantly higher cathodal transport compared to passive flux. Anodal iontophoresis also increased ibuprofen permeation, even though the drug is negatively charged. The application of an electric current for a limited period of time, followed by passive diffusion from the reservoir in

contact with the skin, produced much higher post-iontophoresis fluxes of ibuprofen than passive diffusion.

Lambert et al., Template bleeding time before and at various intervals after ibuprofen lysine dosing of 20 neonatal intensive care unit (NICU) patients. Each bleeding time measured is shown by an 'X'. Lines connect the bleeding times performed before the first dose of ibuprofen with those performed at various preset intervals following the dose.

AIM

To develop a bioequivalent, robust, stable and cost effective formulation of immediate release ibuprofen lysine Tablets 342 & 684mg equivalent in performance to Reference product by direct compression method.

Objective

The objective of the present study is to:

- To develop a formulation of immediate release tablets of ibuprofen lysine of strengths 342mg and 684mg which shall be bioequivalent to Reference product 342mg and 684mg respectively.
- To develop a best processing method using different grades of excipients.
- To develop and evaluate the in-vitro dissolution release of the prepared tablets and to compare with the Reference product.
- To carry out the stability studies of the final formulated product as per the ICH guidelines.
- Data characterization and compilation of the final formulated product.

PLAN OF WORK

- Literature review
- Drug & excipient profile
- Preformulation Studies
    - Evaluation of drug substances
    - Drug-Excipients Compatibility Studies
    - selection of compatible excipients.
- Materials and equipments used
- Formulation trails
- Compression of immediate release tablets
    - Direct Compression (DC grade)

Evaluation of innovator and test product

- Bulk density
- Particle size distribution
- Angle of repose
- Weight variation
- Thickness
- Hardness
- Friability
- Disintegration
- Assay
- Dissolution
- Related Substances

Stability evaluation

- Weight variation, Thickness, Hardness, Friability, Dissolution and Disintegration.
- Assay and Related substance

MATERIALS & METHODS

5.1 Materials used

The following materials are used for the formulation of Ibuprofen lysine tablets

Table No 1: List of materials used for formulation of Ibuprofen lysine tablets

Sl.no	Name of the ingredients	Grade	Function	Source
1	Ibuprofen lysine	USP	Non steroidal anti inflammatory agent	Shasun
2	Sodium starch glycollate	USP/NF	Tablet disintegrant.	DMV Fonterra Excipients
3	Povidone K30	Ph.Eur	Binder	Shasun
4	Magnesium stearate	USP/NF	Lubricant	Nitika
5	Opadry white	IH	Film coating agent	Colorcon
6	Purified water	USP	Vehicle	In house

EQUIPMENTS USED

The following materials are used for the formulation Ibuprofen lysine Tablets

Table No: 2 List of equipments used for formulation Ibuprofen lysine Tablets

S.No	Equipments	Manufacturer
1.	Microscope	Nikon
2.	Digital Vernier Caliper	North Lab
3.	pH Meter	Eutech
4.	Electronic Weighing Scale - 220 g, 320 g,	Sartorious
5.	Multicheck (Hardeness, Thickness and Dimension)	Erweka
6.	Friabilator	Electrolab
7.	Electromagnetic Sieve shaker	Electrolab
8.	Tapped volumeter	Erweka, Germany
9.	Disintegrator	Electrolab
10.	Dissolution apparatus	Electrolab, Mumbai
11.	Mechanical Stirrer	Remi, Mumbai
12.	Hot air Oven	Thermolab
13.	Compression Machine -8 station	Erweka
14.	Coating machine - Conventional	Ideal Cures
15.	Induction sealer	Sigma, Chennai
16.	UV visible spectrophotometer	Shimadzu, Japan
17.	HPLC	Waters, Karnataka
18.	Stability chamber- 40°C/75%RH	Thermolab, Maharashtra
19.	Stability chamber- 50°C/90%RH	Thermolab, Maharashtra

DRUG PROFILE

Name : Ibuprofen Lysine

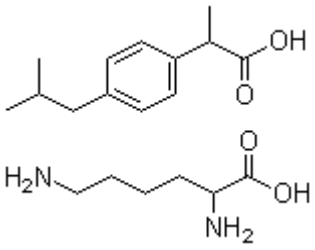
Drug Class **:** Non steroidal anti-inflammatory drug

BCS Class **:** Class I (High solubility and High Permeability)

Chemical Name : Lysine salt of 2(4-isobutylphenyl)propionic acid or (2S)-2,6-diaminohexanoic acid; 2-[4-(2-methylpropyl) phenyl] propanoic acid

Chemical nature **:** Ibuprofen Lysinate is weakly Acid

Chemical structure:



Ionization at different pH:

S.No	pH	% of ionization
1	1	0
2	2	0
3	3	0
4	4	0
5	5	0
6	6	0
7	7	0
8	8	3
9	9	25

Site of absorption : unionized at all pH values; absorption takes place in entire GIT.

Molecular Formula **:** $C_{13}H_{18}O_2.C_6H_{14}N_2O_2$

Molecular weight **:** 352.48

CAS No **:** 57469-76-8

Physical Characterization:

a. **Appearance:** White, crystalline powder or colourless crystals.

b. **Solubility** : It is soluble in water (1%w/v), freely soluble in acetone, in methanol and in methylene chloride. It dissolves in dilute solutions of alkali hydroxides and carbonates

c. **pH of 1 % W/V aqueous solution:** 6.0 - 8.0

d. **Melting point** **:** 178 - 182 °C

e. **Polymorphism** **:** No polymorphism

f. **Chirality** **:** one chiral centre and thus two stereoisomers exist.

g. **Lipophilicity characteristics (Log P):** 3.97

Mechanism of action:

Ibuprofen lysine is the lysine salt of ibuprofen. Ibuprofen is a propionic acid derivative NSAID that has demonstrated its efficacy by inhibition of prostaglandin synthesis. In humans, ibuprofen reduces inflammatory pain, swellings and fever. Furthermore, ibuprofen reversibly inhibits platelet aggregation.

Pharmacokinetic Parameters:

Absorption	Most pharmacokinetic data obtained following the administration of ibuprofen acid also apply to ibuprofen lysine. Ibuprofen is well absorbed from the gastrointestinal tract. Ibuprofen is extensively bound to plasma proteins. Peak serum concentration occurs 1 - 2 hours after administration. However, ibuprofen is more rapidly absorbed from the gastrointestinal tract following the administration of Ibuprofen Lysine 400 mg Tablets, with peak serum concentration occurring approximately 38 minutes after administration
Food Effects	Food does not affect the extent of absorption of Ibuprofen, however, the maximum concentration (C_{max}) is reduced and the time to maximum concentration (t_{max}) is prolonged if Ibuprofen is taken with food.
Distribution	Population Vd of racemic ibuprofen for premature infants at birth is 320 mL/kg.
Metabolism and Distribution	Ibuprofen is metabolised in the liver to two major metabolites with primary excretion via the kidneys, either as such or as major conjugates, together with a negligible amount of unchanged ibuprofen. Excretion by the kidney is both rapid and complete.
Elimination	Elimination half-life is approximately 2 hours. No significant differences in pharmacokinetic profile are observed in the elderly. The t ½ in infants is more than 10 times longer than

	in adults. Interindividual variability in Cl and Vd are 55% and 14%, respectively

Indication:

- Aseptic Necrosis
- Back Pain
- Costochondritis
- Cystic Fibrosis
- Dysautonomia
- Fever
- Frozen Shoulder
- Gout, Acute
- Headache
- Muscle Pain
- Osteoarthritis
- Pain
- Patent Ductus Arteriosus
- Period Pain
- Rheumatoid Arthritis
- Sciatica
- Temporomandibular Joint Disorder

Overdose

Ibuprofen overdose has become common since it was licensed for OTC use. Many overdose experiences are reported in the medical literature, although the frequency of life-threatening complications from ibuprofen overdose is low. Human response in cases of overdose ranges from absence of symptoms to fatal outcome despite intensive-care treatment. Most symptoms are an excess of the pharmacological action of ibuprofen, and include abdominal pain, nausea, vomiting, drowsiness, dizziness, headache, tinnitus, and nystagmus. Rarely,

more severe symptoms, such as gastrointestinal bleeding, seizures, metabolic acidosis, hyperkalaemia, hypotension, bradycardia, tachycardia, atrial fibrillation, coma, hepatic dysfunction, acute renal failure, cyanosis, respiratory depression, and cardiac arrest have been reported. The severity of symptoms varies with the ingested dose and the time elapsed; however, individual sensitivity also plays an important role. Generally, the symptoms observed with an overdose of ibuprofen are similar to the symptoms caused by overdoses of other NSAIDs.

Adverse effects

Common adverse effects include: nausea, dyspepsia, gastrointestinal ulceration/bleeding, raised liver enzymes, diarrhea, constipation, epistaxis, headache, dizziness, priapism, rash, salt and fluid retention, and hypertension. A study from 2010 has shown regular use of NSAIDs was associated with an increase in hearing loss.

SODIUM STARCH GLYCOLATE

Nonproprietary Names

- BP: Sodium starch glycollate
- PhEur: Carboxymethylamylum natricum
- USPNF: Sodium starch glycolate

Synonyms

Carboxy methyl starch, sodium salt; starch carboxy methyl ether, sodium salt;

Chemical Name

Sodium carboxy methyl starch

Functional Category

Tablet disintegrants.

Applications in Pharmaceutical Formulation or Technology

Sodium starch glycolate is used in oral pharmaceuticals as a disintegrant in tablet formulations.

Description

Sodium starch glycolate is a white to off-white, odorless, tasteless, free-flowing powder. Sparingly soluble in ethanol (95%) and practically insoluble in water.

Stability and Storage Conditions

It is stable and should be stored in a well-closed container in order to protect it from wide variations of humidity and temperature, which may cause caking.

Incompatibilities

Sodium starch glycolate is incompatible with ascorbic acid.

Safety

Sodium starch glycolate oral ingestion of large quantities may be harmful.

POVIDONE

Nonproprietary Names

BP: Povidone

JP: Povidone

PhEur: Povidonum

USP: Povidone

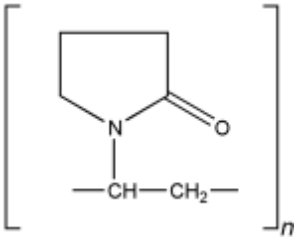
Synonyms

poly [1-(2-oxo-1-pyrrolidinyl)ethylene]; polyvidone; polyvinylpyrrolidone; PVP; 1-vinyl-2-pyrrolidinone polymer.

Chemical Name

1-Ethenyl-2-pyrrolidinone homopolymer

Empirical Formula

$(C_6H_9NO)_n$ 

Functional Category

Disintegrant, dissolution aid, suspending agent and tablet binder.

Applications in Pharmaceutical Formulation or Technology

In tableting, Povidone is used as binders in wet-granulation processes and as coating agents.

Description

Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder and freely soluble in acids, chloroform, methanol, and water practically insoluble in ether, hydrocarbons and mineral oil.

Stability and Storage Conditions

The powder is hygroscopic; it should be stored in an airtight container in a cool, dry place.

Incompatibilities

Povidone is compatible in solution with a wide range of inorganic salts, natural and synthetic resins, and other chemicals.

Safety

Povidone may be regarded as nontoxic since it is not absorbed from the gastrointestinal tract or mucous membranes.

MAGNESIUM STEARATE

Nonproprietary Names

- BP: Magnesium stearate
- JP: Magnesium stearate
- PhEur: Magnesii stearas
- USPNF: Magnesium stearate

Synonyms

Magnesium octadecanoate, octadecanoic acid, magnesium salt, stearic acid, magnesium salt.

Chemical Name

Octadecanoic acid magnesium salt

Empirical Formula

$C_{36}H_{70}MgO_4$

Functional Category

Tablet lubricant.

Applications in Pharmaceutical Formulation or Technology

Magnesium stearate is widely used as a lubricant.

Description

It is a very fine, light white, precipitated powder of low bulk density, having a faint odor of stearic acid with a characteristic taste and greasy to the touch and readily adheres to the skin. Practically insoluble in ethanol, ether and water; slightly soluble in warm benzene.

Stability and Storage Conditions

Magnesium stearate is stable and should be stored in a well-closed container in a cool, dry place.

Incompatibilities

Incompatible with strong acids, alkalis, iron salts and strong oxidizing materials.

Safety

Oral consumption of large quantities may produce a laxative effect or mucosal irritation.

OPADRY WHITE

Material description:

White powder

Ingredients:

i. Titanium dioxide
ii. Polyethylene glycol/ Macrogol
iii. Hypromellose
iv. Elemental Iron content:0.0%

Table No: 3 Test of opadry white

S.No	Tests	Minimum	Maximum	Result
1.	Ash,%	26.00	36.00	31.08
2.	Colour difference	0.0	1.5	1.5
3.	Appearance	White powder		

Application: as a film coating agent for tablets.

EXPERIMENTAL INVESTIGATIONS

Preformulation studies:

API Characterization

Pre-formulation studies were performed on the drug which includes solubility, Bulk density, Tapped density, Compatibility.

2 Solubility

Solubility is the property of a solid, liquid, or gaseous chemical substance called solute to dissolve in a liquid solvent to form a homogeneous solution of the solute of the solute in the solvent. The solubility of a substance fundamentally depends on the used solvent as well as on temperature and pressure. The specified quantity of sample (1gm) was added into different quantity of solvent (methanol, alcohol, chloroform, water, acetone, ethyl acetate) in room temperature.

Bulk density:

Bulk density is the ratio of the weight of the powder to the bulk volume it occupies. it is expressed in gm/ml. Weighed quantity of granules was transferred into a 50 ml measuring cylinder without tapping, during transfer the volume occupied by granules was measured. Bulk density was measured by using formula.

$$P = m/V_o$$

Where,

P_i = Bulk density

m = Mass of the blend,

V_o= Untapped Volume

Tapped Density:

Weighed quantity of granules was taken into graduated cylinder, volume occupied by granules was noted down. Then cylinder was subjected to 500 taps in tapped density tester (Electro Lab USP II), the % Volume variation was calculated by following formula.

$$P_t = m/V_i$$

Where,

P_t = Tapped density

M = Mass of the blend,

V_i= Tapped volume

Carr's compressibility index:

Compressibility is the ability of powder to decrease in volume under pressure. Using untapped density and tapped density the percentage compressibility of granules were determined, which is given as Carr's compressibility index.

$$CI = V_i - V_0 / V_i \times 100$$

Where,

CI = Compressibility index

Vo = Bulk density

V_i = Tapped density

Table: 4 Compressibility index

Compressibility index (%)	Flow characters
< 10	Excellent
11-15	Good
16-20	Fair
21-25	Possible
26-31	Poor
> 32	Very poor

Hausner's Ratio:

It is measurement of frictional resistance of the drug. It was determined by the ratio of tapped density and bulk density.

Hausner's Ratio = Vo/V_i

Where,

Vo = Bulk density

V_i = Tapped density

Table No: 5 **Hausner's ratio**

Flow characters	Hausner's ratio
Excellent	1.11
Good	1.12 – 1.18
Fair	1.19 – 1.25
Possible	1.26 – 1.34
Poor	1.35 – 1.45
Very poor	1.46 – 1.59
Very Very poor	>1.60

Physical Appearance:

The API was observed for its colour and physical state

Particle size distribution (PSD):

PSD is determined by stacking the sieves on top of one another in ascending degree of coarseness (#20, #40, #60, #80, #100) and then placing the 100 g of test sample on the top sieve (20#).The nest of sieves is subjected to 10 minutes period of agitation and then the weight retained on each sieve is accurately determined and expressed in terms of percentage

Drug excipients compatibility studies by HPLC

The successful formulation of a stable and effective solid dosage form depends on the careful selection of the excipients that are added. The commonly used excipients are mixed with the API in the different ratios and subjected to accelerated condition (3 months in 40°C / 75 % RH) and at stress condition (1 month in 50°C / 90 % RH) the sample are monitored for any change in physical state, colour, odour, loss on drying and related substances. Any excipients contributing to such a change shall not be used in the formulation.

Selection of excipients

Excipients are selected based on the excipients of reference product apart from the reference product, other excipients are selected based on the possible use of them.

Stability study:

Sample preparation

The mixtures of the drug and excipients are prepared by placing the accurately weighed amounts of the drug and excipients in polybag and mixed till homogenous mixture is achieved. Then these mixtures are filled in vials and closed with bromo butyl rubber stoppers & crimped with tear off clear lacquer aluminum seals. These samples are charged at 50°C/90% RH and 40°C/75% RH conditions.

Table No: 6 Storage condition and sampling interval

S.NO	Storage condition	Samples packed in	Sampling interval
1	Accelerated condition (40°C/75% RH)	Type 1 glass vials	1M, 2M and 3M
2	Stressed condition (50 C/90% RH)	Type 1 glass vials	I5 days and 1M

Formulation development:

The development was started with direct compression process using the directly compressible grade excipients.

Direct compression

Figure No: 1 Process Flow Diagram of direct compression

Formulation trials by direct compression technique Procedure for direct compression process

1.The desired quantities were weighed & dispensed.

2. Drug substance and Excipients were sifted through #40mesh, Magnesium stearate was sifted through #60mesh.

3. Drug substance with excipients was blended in polybagfor 5 min.

4. Lubricant were added in polybagwith the above blend and blended for 3 min.

5. Evaluations of blend.

6. The blend was compressed in the 8-station compression machine Erweka TR-D8 with suitable toolings.

7. Evaluation of tablets.

Table No:7 Composition of ibuprofen lysine 342mg strength (F1,F2,F3, F4, F5 and F6 trials)

Ingredients (mg/tab)	Mg/tablet					
	F1	**F2**	**F3**	**F4**	**F5 (Reproducibility Batch)**	**F6 (Scale up batch)**
Ibuprofen lysine	342	342	342	342	342	342
Povidone K 30	7	17	10	10.000	10	10
Sodium starch glycolate	25	25	36	31.000	31	31
Magnesium stearate	6	6	7	12.000	12	12
Core tablet weight (mg)	370	380	395	395	395	395
Opadry white	*	*	*	11.85	11.85	11.85
Purified Water	*	*	*	q.s	q.s	q.s
Total weight (mg)	*	*	*	406.85	406.85	406.85
Batch size	750gm	750 gm	750 gm	750gm	1500gm	3000gm

Table No: 8 Composition of ibuprofen lysine 684mg strength (F7, F8, F9 and F10 trials)

Ingredients (mg/tab)	Mg/tablet			
	F7	F8	F9 (Reproducibility Batch)	F10 (Scale up batch)
Ibuprofen lysine	684	684	684	684
Povidone K 30	30	20	20	20
Sodium starch glycolate	55	62.000	62.000	62.000
Magnesium stearate	21	24.000	24.000	24.000
Core tablet weight (mg)	790	790	790	790
Opadry white	*	23.7	23.7	23.7
Purified Water	*	q.s	q.s	q.s
Total weight (mg)	*	813.7	813.7	813.7
Batch size	750gm	750gm	1500gm	3000gm

Manufacturing process – Direct compression

The following steps are involved in the manufacturing of ibuprofen lysine tablets

1. Dispensing of all ingredients
2. Sifting of all ingredients
3. Blending

4. Compression
5. Coating

1.Dispensing :

In this step the API and other excipients were dispensed as per the quantity mentioned table. The API and all excipient were taken in individual self seal cover.

2.Shifting:

- Ibuprofen lysine & povidone were co-sifted through #40mesh
- Sodium starch glycollate were passed through # 40 mesh.
- Magnesium stearate passed through the # 60 mesh.

3.Blending:

Equipment : V. Blender

Process :

- Ibuprofen lysine , povidone k30 and Sodium starch glycollate were loaded inV.blender for 5 minutes at slow speed.
- Magnesium stearate is added for 3 minutes at slow speed

4.Compression

Make :Erweka TR-D8 (8 Station)

Punch description	**For 342mg**	**For 684mg**
Dimension	14.4 × 8.7 mm	19 × 8.7
Upper punch	plain	

Lower punch	plain

5.Coating:

Table No: Coating parameters for ibuprofen lysine Tablets 25mg

S.No	Parameters	Set parameters
1	Nozzle diameter of spray gun	1.0 mm
2	Distance between the tablet bed and spray nozzle	15 cm
3	Peristaltic pump	1.0 RPM
4	Tablet bed temperature	41°C - 43°C
5	Inlet air temperature	65°C
6	Atomizing air pressure	2.0 Kg/cm^2
7	RPM of the coating pan	10-20 RPM

Preparation of Film coating solution:

The film coating solution was prepared by simple solution method. It was prepared by opadry white (Polyvinyl alcohol, Titanium dioxide, polyethylene glycol and Talc.) dissolved in weighed quantity of purified water. This was stirred for 45 minutes until get a uniform mixture was obtained. Then it was sifted through #100 screen and used for coating of core tablets.

Coating procedure:

The compressed tablets were loaded in pan, and start to dry warming for 15 mins at slow speed. Then take 50 numbers of warmed tablets, and note down the average weight of the tablets. Solid dispersion is 12% and coating is done until tablets attain weight build up is 3%.

Evaluation of tablets

Evaluation of physical characteristics :

The formulated tablets were evaluated for the following physicochemical parameters,

Thickness:

Thickness mainly depends on die filling, physical properties of material to be compressed under compression force. There is bound to be a small variation in the thickness of individual tablet in a batch. But it should not be apparent to the unaided eye. The thickness and diameter were measured by using vernier calipers.

Hardness:

Tablet requires certain amount of strength or hardness, measured by Monsanto hardness tester. Ten tablets were randomly picked from each formulation and evaluated for hardness during manufacturing and is expressed in N.

Friability:

Friability was performed by using Roche friabilator, normally pre weighed ten tablets were placed in the plastic chamber of friabilator. This was then operated for 100 revolutions. Tablets dropping from a distance of six

inches with each revolution. Tablets are then dusted and reweighed. Loss of less than 1% in weight is considered to be acceptable.

$$F(\%) = \frac{Initial\ wt. - Final\ weight}{Initial\ wt}$$

Weight variation test:

Twenty tablets were selected randomly and weighed individually. Calculate average weight and compare the individual tablet weight to the average. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in table and none deviate by more than twice the percentage.

Disintegration test:

The disintegration time was measured by using usp disintegration test apparatus six tablets were placed in the tube and the basket was kept in 1 litre beaker of purified water maintained at 37 ^{0}**C** the basket containing tablets move up and down through a distance of 5 to 6cm at a frequency of 28 to 32 cycles per minute .the specific time tablet is disintegrate completely was noted.

Dissolution studies:

Dissolution by HPLC:

Reagents/chemicals:

Potassium dihydrogen orthophosphate	:	AR Grade
Acetonitrile	:	HPLC Grade
Glacial acetic acid	:	AR Grade
Sodium hydroxide	:	AR Grade
Triethylamine	:	AR Grade
Water	:	Purified water/ Milli-Q /HPLC water

Dissolution Medium Preparation:

Dissolve 68.0 g of potassium dihydrogen orthophosphate and 9.0 g of sodium hydroxide in 10000 mL of purified water and mix. Check and adjust to the pH to 6.8 ± 0.05

Dissolution Parameters:

Apparatus : USP Type II (Paddle)

Medium : pH 6.8 Phosphate buffer

Volume : 900 mL

Rotational speed : 50 RPM

Temperature : 37.0 ± 0.5°C

Time : 5, 10, 15, 20, 30, 45 & 60 minutes or as required.

Preparation of mobile phase:

Mix 600 mL of acetonitrile, 400 mL of HPLC water, 1mL of glacial acetic acid and 0.2 mL of triethylamine, filter through 0.45µm membrane filter and degas.

Chromatographic conditions:

Column	:	Hypersil BDS C18 150 x 4.6 mm, 5 µm
Flow rate	:	1.0 mL/min
Column temperature	:	Ambient
Wavelength	:	220 nm
Injection volume	:	5 µL
Pump mode	:	Isocratic
Run time	:	12 minutes

Preparation of solutions:

Preparation of standard solution for 342 mg:

Weigh accurately about 47.5 mg of Ibuprofen Lysine reference/working standard into a 25 mL volumetric flask. add 10 mL of water and sonicate to dissolve and make up the volume up to the mark with water and mix.

Then dilute 5 mL of solution to 25 mL volumetric flask with dissolution medium (380 µg/mL of Ibuprofen Lysine).

Preparation of standard solution for 684 mg:

Weigh accurately about 47.5 mg of Ibuprofen Lysine reference/working standard into a 25 mL volumetric flask. add 10 mL of water and sonicate to dissolve and make up the volume up to the mark with water and mix.

Then dilute 10 mL of solution to 25 mL volumetric flask with dissolution medium (760 µg/mL of Ibuprofen Lysine).

Preparation of sample solution:

Set the parameters of dissolution apparatus as per test method procedure. Place previously weighed six tablets in each of the six dissolution vessels and start the dissolution test. At the end of specified time, withdraw the sample from each of

the dissolution vessel. Filter the solution through 0.45 µm nylon membrane filter discarding the first few mL of filtrate.

Procedure:

Inject the following solutions and record the chromatogram. The retention time of Ibuprofen Lysine is about 4.9 minutes.

Table No: 9

S. No	Solutions	No. of Injections
1	Blank (dissolution medium)	1
2	Standard solution	1
4	Sample solution	1

Evaluation of system suitability:

1. The relative standard deviation for five replicate standard 2 areas should not be more

than 2.0%

2. The tailing factor for Ibuprofen Lysine peak should not be more than 2.0.

3. The theoretical plates for Ibuprofen Lysine peak should not be less than 5000.

Calculation:

1. Similarity factor:

$$\frac{\text{Area of Standard solution - 1}}{\text{Area of Standard solution – 2 (First injection)}} \quad \frac{\text{Weight of Standard solution - 2}}{\text{Weight of Standard solution - 1}}$$

2. % Drug release:

For 342 mg:

$$\% \text{ drug release} = \frac{A_{sam}}{A_{std}} \times \frac{\text{Std Wt.}}{25} \times \frac{5}{25} \times \frac{900}{LC} \times \frac{P}{100} \times 100$$

Where,

A_{sam} : Area of Ibuprofen Lysine peak in the sample chromatogram

A_{Std} : Average area of Ibuprofen Lysine peak in the standard -2 chromatogram

Std Wt. : Weight of Ibuprofen Lysine reference / working standard taken in mg

LC : Label claim in mg

P : Percentage potency of Ibuprofen Lysine reference / working standard on as is basis

For 684 mg:

$$\% \text{ drug release} = \frac{A_{sam}}{A_{std}} \times \frac{\text{Std Wt.}}{25} \times \frac{10}{25} \times \frac{900}{LC} \times \frac{P}{100} \times 100$$

Where,

A_{sam} : Area of Ibuprofen Lysine peak in the sample chromatogram

A_{Std} : Average area of Ibuprofen Lysine peak in the standard -2 chromatogram

Std Wt. : Weight of Ibuprofen Lysine reference / working standard taken in mg

LC : Label claim in mg

P : Percentage potency of Ibuprofen Lysine reference / working standard on as is basis

Content uniformity:

Assay by HPLC:

Reagents/Chemicals:

Mono chloro Acetic acid	: AR grade
Ammonium Hydroxide	: GR grade
Acetonitrile	: HPLC grade
Water	: HPLC grade

Chromatographic conditions:

Column	: Hypersil ODS, 150x4.6mm, 5µm
Part No	: 30105-154630
Column oven temperature	: 25°C
Flow rate	: 1.0ml/min
Injection volume	: 5.0µL
Wavelength	: 220nm

Run time : 10 minutes

Pump mode : Isocratic

Preparation of mobile phase:

Dissolve 4.0g of mono chloro acetic acid in 400ml of water and adjust the pH to 3.00 ± 0.05 with ammonium hydroxide. Add 600ml of acetonitrile filter and degas.

Diluent:

Mixed water and acetonitrile in the ratio of 50:50%v/v.

Preparation of solutions:

Standard solution

Weigh accurately about 50.0 mg of Ibuprofen Lysine In-house reference standard into a 50 ml volumetric flask, add 30 ml of diluents and sonicate to dissolve and make up the volume up to the mark with diluents and mix.

Then dilute 5 ml of solution to 50ml volumetric flask with diluent (Conc: 100ppm)

Sample preparation:

Weigh 20 tablets and crush in a mortar to get a find powder. Accurately weigh and transfer powder equivalent to 500mg of Ibuprofen Lysine into a 250ml volumetric flask. Add about 125ml of water and sonicate for 10 minutes with

intermittent shaking, add about 75 ml of acetonitrile and sonicae for 20 minutes, cool the solution to room temperature and make the volume up to the mark with acetonitrile and mix. Filter the solution through 0.45µm nylon filter. Dilute 5ml of the filtrate to 100ml volumetric flask with diluent (Conc: 100ppm).

Procedure:

Inject the blank, standard and sample solution in the sequence as given in the below table

Table No: 10

S.No.	Solution	No of Injections
1	Blank	1
2	Standard solution-1	1
3	Sample solution	2

Calculations:

Calculate the % content of Ibuprofen Lysine in the tablets by using the following Formula

$$= \frac{AT}{AS} \times \frac{Ws}{50} \times \frac{5}{50} \times \frac{250}{Wt} \times \frac{100}{5} \times \frac{Avg.wt}{LC} \times P$$

Where,

AT = Average area of Ibuprofen Lysine in the chromatogram of sample solution.

AS = Average area of Ibuprofen Lysine in the chromatogram standard solution-2

Ws = Weight in mg of Ibuprofen Lysine In-house reference standard

Wt = Weight of sample taken in mg

Avg.wt = Average weight in mg

LC = Label claim in mg

P = % Purity of Ibuprofen Lysine In-house reference standard

Stability studies:

As per in vitro release formulation F6, F10 was found to be desirable than other formulation. Hence it was chosen for stability studies. The tablets were packed in PVC/PVDC blisters and kept for 15 days and 1 month at 50ºC/90%RH and for 1M, 2M and 3M at 40C/75%RH in a stability chamber at the interval of mentioned period, tablets were withdrawn and evaluated for physical properties like weight variation, thickness, hardness, and invitro drug release was also carried out.

RESULTS AND DISCUSSION

Table No:11 Evaluation of RLD

S.No.	TESTS	LIMITS	
		342 mg	**684 mg**
1	Description	Almost white colored, film coated, caplet shaped tablets and printed NMP on one side	
2	Identification A) By HPLC	The retention time of ibuprofen lysine peak obtained from the chromatogram of sample preparation corresponds to that of the chromatogram of similar preparation of standard as obtained in the assay.	
3	Average wt in (mg)	403.31	817.93
4	Average thickness (in mm)	Minimum 4.55 – maximum 4.69	Minimum 6.51 – maximum 6.69
5	Disintegration test	Minimum7.50 – maximum 8.36	Minimum10.20 – maximum 13.01
6	water content by KF (% w/w)	1.39	1.44
7	Assay by HPLC on dried basis (% w/w)	97.8	100.1
8	Dissolution (% amount of drug dissolved in 45 mins)	Minimum 103 – maximum 106 Average-105	Minimum 99– maximum 104 Average-102

9	Related substances by HPLC(% w/w) 2-[3-(2-methylpropyl) phenyl] propanoic Acid (impurity A) 2-(-n-butylphenyl) propionic acid (impurity B) (2RS)-2-hydroxy-2-[4-(2- methyl propyl) phenyl] propanoic acid.	0.02 0.01 0.02	0.03 0.01 0.06
10	Highest unknown	0.02	0.02
11	Total impurities	0.08	0.12

Reference product Details

Table No: 12

Brand name	Ibuprofen Lysine Tablets
Manufacturer / distributor	Reckitt Benckiser Healthcare (UK) Ltd / Crookes Healthcare Limited
Strengths available	342mg and 684mg
RLD strength	684 mg
684mg	Opaque, white with N684 mark on one face.
342mg	Opaque, white with an identifying logo in black on one face.
Composition	Ibuprofen Lysine 684/342 mg/tablet (equivalent to 400/200 mg Ibuprofen)
1	Povidone
2	Sodium starch glycolate
3	Magnesium stearate
4	Hypromellose
5	Talc
6	Opaspray White M-1-7111B (contains hypromellose and Titanium dioxide (E171))
7	Opacode Black S-1-8152HV (contains “black” iron oxide (E172), shellac, soya lecithin and Antifoam DC 1510).
Packing details	The blisters are packed in cardboard cartons. Pack sizes: 4, 6, 8,12,16 and 24 tablets
684mg	
342mg	
Storage condition	Do not store above 30ºC. Store tablets in the original packaging.

DRUG-EXCIPIENTS COMPATIBILITY STUDY

Table No: 13 Drug-Excipient Compatibility Chart

Drug: Excipients proportion	Ratio	Stability Condition	Imp A (%)	Imp B (%)	Imp C (%)	Imp D (%)	Unknown Imp E (%)	Total Impurity (%)
API	-	INITIAL	ND	ND	ND	0.02	ND	**0.05**
		40°C/75%RH-1M	ND	ND	ND	0.02	ND	**0.04**
		40°C/75%RH-2M	ND	ND	0.01	0.03	0.01	**0.04**
		40°C/75%RH-3M	ND	ND	0.01	0.03	ND	**0.06**
		50°C/90%RH-1M	ND	ND	ND	0.02	ND	**0.06**
API+ Povidone K 30	1:1	INITIAL	ND	ND	0.01	0.02	ND	**0.05**
		40°C/75%RH-1M	ND	ND	0.01	0.02	ND	**0.04**
		40°C/75%RH-2M	ND	ND	0.01	0.03	ND	**0.07**
		40°C/75%RH-3M	ND	ND	0.01	0.02	0.02	**0.16**
		50°C/90%RH-1M	ND	ND	ND	0.02	ND	**0.06**
API+ Sodium starch glycolate	1:1	INITIAL	ND	ND	0.01	0.03	ND	**0.05**
		40°C/75%RH-1M	ND	ND	ND	0.02	ND	**0.04**
		40°C/75%RH-2M	0.01	ND	0.01	0.03	ND	**0.07**
		40°C/75%RH-3M	ND	ND	0.01	0.02	0.02	**0.16**
		50°C/90%RH-1M	0.01	ND	ND	0.02	ND	**0.06**
API+ Magnesium stearate	1:1	INITIAL	ND	ND	0.01	0.03	ND	**0.05**
		40°C/75%RH-1M	ND	ND	0.01	0.02	0.01	**0.05**
		40°C/75%RH-2M	ND	ND	0.01	0.03	ND	**0.05**
		40°C/75%RH-3M	ND	ND	0.01	0.03	ND	**0.06**
		50°C/90%RH-1M	ND	ND	ND	0.02	ND	**0.03**
API+Povidone K 30 + Sodium starch glycolate + Magnesium stearate	mixture	INITIAL	ND	ND	ND	0.02	ND	**0.04**
		40°C/75%RH-1M	ND	ND	0.01	0.03	ND	**0.05**
		40°C/75%RH-2M	ND	ND	0.01	0.03	ND	**0.06**
		40°C/75%RH-3M	ND	ND	0.01	0.03	ND	**0.06**
		50°C/90%RH-1M	ND	ND	0.01	0.03	ND	**0.06**
Povidone K 30 + Sodium starch glycolate + Magnesium stearate	mixture	INITIAL	ND	ND	0.01	0.03	ND	**0.05**
		40°C/75%RH-1M	ND	ND	0.01	0.02	0.01	**0.04**
		40°C/75%RH-2M	ND	ND	0.01	0.03	ND	**0.05**
		40°C/75%RH-3M	ND	ND	0.01	0.03	ND	**0.06**
		50°C/90%RH-1M	ND	ND	ND	0.02	ND	**0.03**
API+ Opadry II White	1:1	INITIAL	ND	ND	0.01	0.03	ND	**0.05**
		40°C/75%RH-1M	ND	ND	ND	0.02	0.01	**0.04**
		40°C/75%RH-2M	ND	ND	ND	0.02	0.01	**0.05**
		40°C/75%RH-3M	ND	ND	0.01	0.03	ND	**0.06**
		50°C/90%RH-1M	ND	ND	ND	0.02	ND	**0.03**

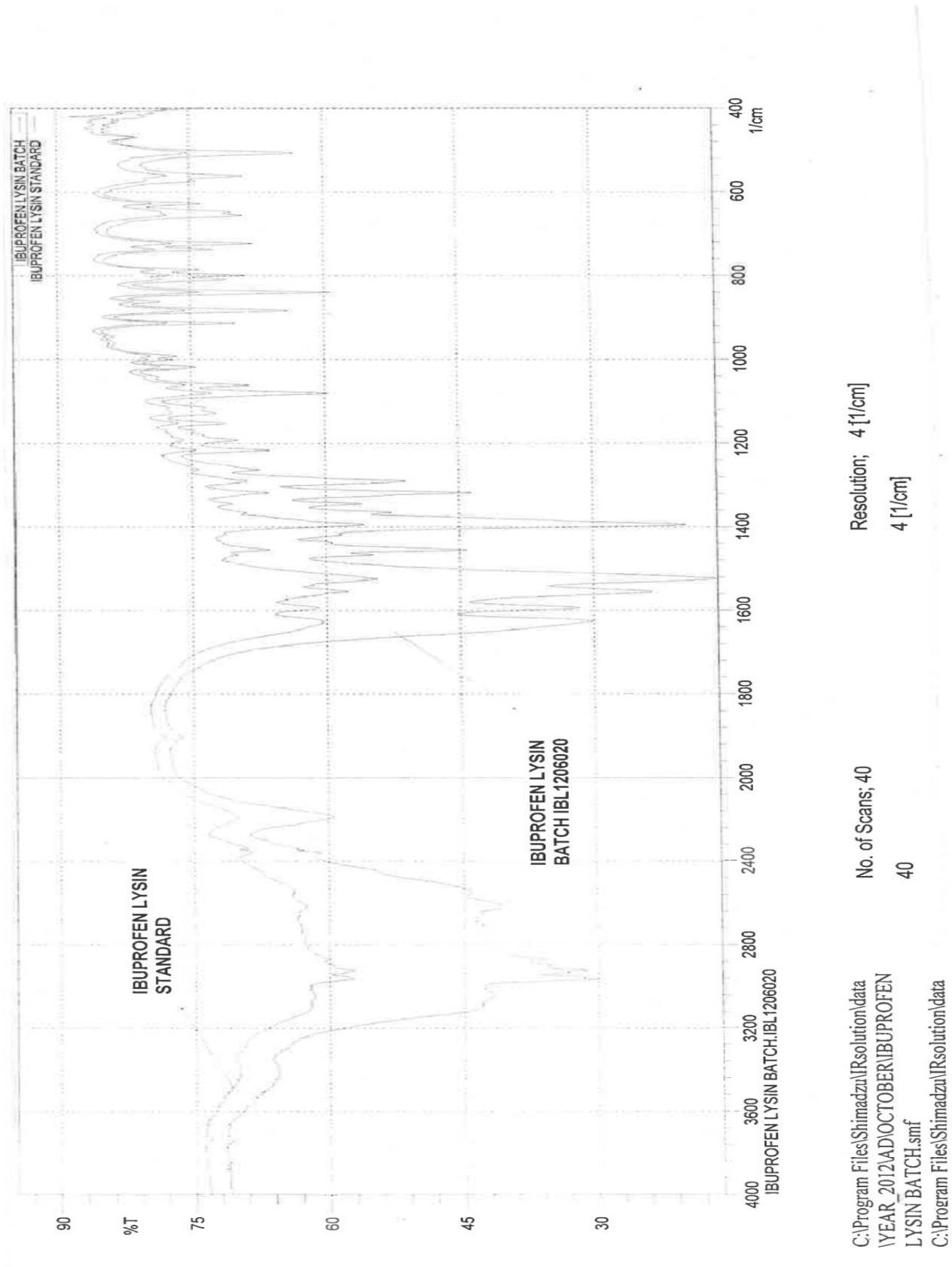
Table No: 14 Impurities and Limits

IMPURITIES	LIMITS

Impurity A	Not more than 0.15%
Impurity B	Not more than 0.15%
Impurity C	Not more than 0.15%
Impurity D	Not more than 0.15%
Impurity E	Not more than 0.10%
Total impurities	Not more than 0.5%

Observation and Conclusion

All the excipients used in the Drug-Excipients compatibility study were found to be compatible and the Impurities were within the limits. Hence further formulation development studies are proceeded.


IBUPROFEN LYSIN BATCH
IBUPROFEN LYSIN STANDARD
IBUPROFEN LYSIN STANDARD
IBUPROFEN LYSIN BATCH IBL1206020
%T
90
75
60
45
30
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
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1/cm
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LYSIN BATCH.smf
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DISSOLUTION PROFILE OF REFERENCE PRODUCTS

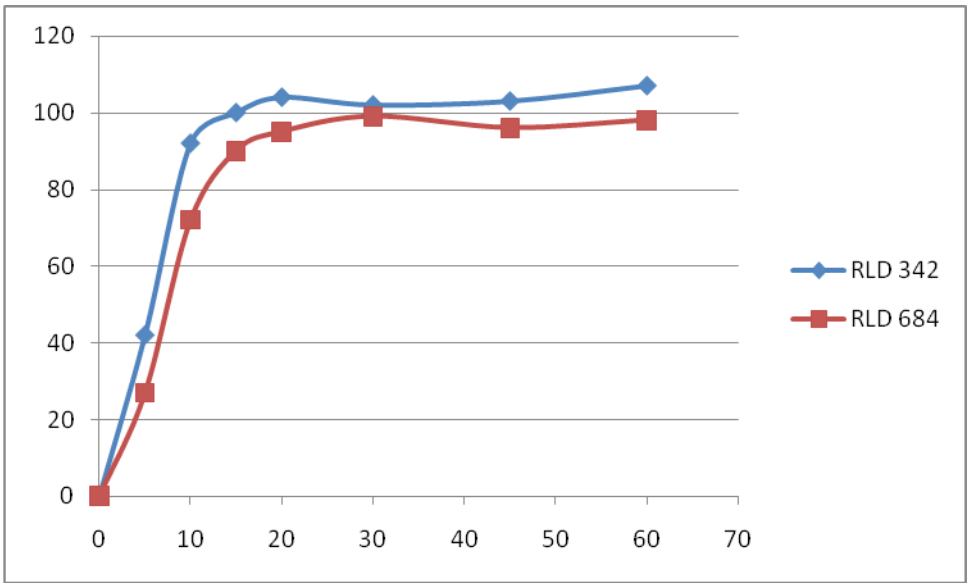
Ibuprufen lysine is not published in any of the official monograph and hence to analyze and confirm the Reference products dissolution characters, the both strengths of the Reference products tablets are analyzed in 3 different Media.

I. Dissolution profiles in Reference products Purified water

Table No: 15 Dissolution profiles of the Reference products in Purified water

Type	USP Type - II (Paddle)	
RPM	50	
Temp 37°C ± 0.5°C		
Volume	900 ml	
Media	Purified water	
Method:	HPLC	
Time in minutes	**% Drug Release in Purified water**	
	342 mg	**684 mg**
5	42	27
10	92	72
15	100	90
20	104	95
30	102	99
45	103	96
60	107	98

Figure No: 2 Dissolution graph of the Reference products in Purified water



II. Dissolution profiles in 0.1N HCl

Table No: 16 Dissolution profiles of the Reference products in 0.1N HCl

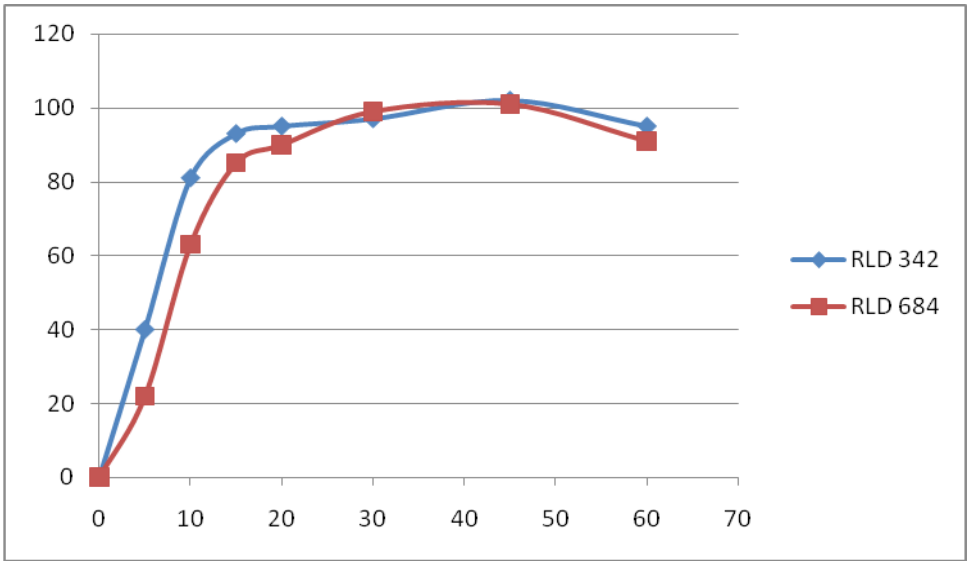
Type	USP Type - II (Paddle)	
RPM	50	
Temp	37ºC ± 0.5˚C	
Volume	900 ml	
Media	0.1N HCl	
Method:	**HPLC**	
% Drug Release in 0.1N HCl **Time in minutes**	**342 mg**	
	26	27
10	78	72
15	96	89
20	99	94
30	101	100
45	101	98
60	101	98

III. Dissolution profiles in pH 6.8 Buffer

Table No: 17 Dissolution profiles of the Reference products in pH 6.8 Buffer

Type	USP Type - II (Paddle)	
RPM	50	
Temp 37°C ± 0.5°C		
Volume	900 ml	
Media	pH 6.8 Buffer	
Method:	HPLC	
Time in minutes	**% Drug Release in pH 6.8 Buffer**	
	342mg	**684 mg**
5	44	22
10	86	63
15	95	85
20	97	90
30	98	99
45	98	101
60	99	91

Figure No: 4 Dissolution graph of the Reference product in pH 4.5 Buffer



Observation and disscusion

The two strength released ≥ 85% of the drug with in 15 minutes in Purified water, 0.1N HCl and pH 6.5 Buffer. The dissolution profile results obtained in the 3 media for the two strength are kept as the standard reference for the evaluation in further dissolution studies.

EVALUATION OF FORMULATION TRIALS

DIRECT COMPRESSION

Ibuprofen lysine Tablets 342mg

Table No: 18 Characteristics of the Formulation trial–F1 blend

S.No	Parameters	Results
1	Description/Appearance	White coloured powder blend
2	Bulk density (g/ml)	0.50
3	Tapped density (g/ml)	0.68
4	Carr's Index (%)	26
5	Hausner's Ratio	1.36
6	Flow property	Poor

Observation

The Carr's index and the Hausner's Ratio indicated that the blend has poor flow characters. To understand the powder behaviour the batch was taken further for compression.

It was observed that the blend had formed a cake in the feed frame and there were weight variations due to non uniformity of the powder flow.

disscusion

It was plan to increase the binder concentration for the better compressibility

Ibuprofen lysine Tablets 342mg strengths

Table No: 19 Characteristics of the Formulation trial–F2 blend

S.No	Parameters	Results
1	Description/Appearance	White coloured powder blend
2	Bulk density (g/ml)	0.55
3	Tapped density (g/ml)	0.62
4	Carr's Index (%)	11.290
5	Hausner's Ratio	1.127
6	Flow property	Possible

Observation:

The Carr's index and the Hausner's Ratio indicated that the blend has Passable flow characters.

It was observed that the blend had formed rat hole and chocked in the feed frame and there were weight variations due to non uniformity of the powder flow.

Hardness was high but Disintegration was more than 16mts

Discussion:

It was planned to decrease the binder concentration for lesser Disintegration time and to addition of lubricants for overcome the rat hole.

.

Ibuprufen lysine Tablets 342mg

Table No: 20 Characteristics of the Formulation trial–F3, F4, F5 & F6 blend

S.No	PARAMETERS	F3	F4	F5 (Reproducibility batch)	F6 (scale up batch)
1.	Bulk density (g/ml)	0.47	0.45	0.44	0.45
2.	Tapped density (g/ml)	0.59	0.56	0.56	0.56
3.	Carr's index (%)	20.34	19.64	21.42	19.64
4.	Hausner's ratio	1.26	1.24	1.27	1.24
5.	Flow property	Passable	Fair	Passable	Fair
Particle size distribution					
	Sieve Analysis	**Cumulative % Retained**			
		F3	**F4**	**F5**	**Finalized batch**
1.	# 40 mesh retention	37.00	33.00	35.00	34.00
2.	# 60 mesh retention	57.00	51.00	52.00	51.00
3.	# 80 mesh retention	69.00	67.00	66.00	66.00
4.	# 100 mesh retention	79.00	76.00	75.00	76.00
5.	# PAN	100.00	100.00	100.00	100.00

Observation and Conclusion

Among the formulation trials ,F3 were found to be slightly coarser in nature. The remaining trials showed comparative reproducibility.

CORE TABLETS					
S.No	**PARAMETERS**	**F3**	**F4**	**F5 (Reproducibility batch)**	**F6 (scale up batch)**
1.	Average Weight (mg)	387.85	386.89	385.40	386.33
2.	Thickness (mm)	3.39	3.41	5.50	3.57
3.	Hardness (N)	122	128	133	136
4.	Friability (% w/w)	0.06%	0.02%	0.02%	0.02%
5.	Disintegration Time (min & sec)	3 min 20sec	6min15sec-6mins 50 sec	6min 20sec-6mins 58 sec	6mins 31 sec- 6 mins 46sec
COATED TABLETS					
6	Thickness(mm)	-	4.51	4.55	4.60
7	Disintegration time (min & sec)	-	7min05sec	7min 20sec-7mins 58 sec	7mins 31 sec- 7mins 46sec

Table No: 21 Parameters of the Formulation trial – F3, F4, F5 & F6

DISSOLUTION PROFILE

Formulation trial- F3

Table No: 22 Comparative Dissolution Profile of (F3) core tablet 342 mg in pH 6.8 Buffer

Type	USP Type - II (Paddle)		
RPM	50		
Temp	37°C ± 0.5°C		
Volume 900 ml			
Media	pH 6.8 Buffer		
Method:	HPLC		
S.No	**Time (minutes)**	**% Drug Release** **Reference product Tablets 342mg**	**Formula -F3 (core tablet 342mg strength)**
1.	5	44	58
2.	10	86	86
3.	15	95	90
4.	20	97	91
5.	30	98	91
6.	45	98	90
7.	60	99	90
Dissimilarity factor & Similarity factor			
f1 value = 7.94		f2 value = 56.72	

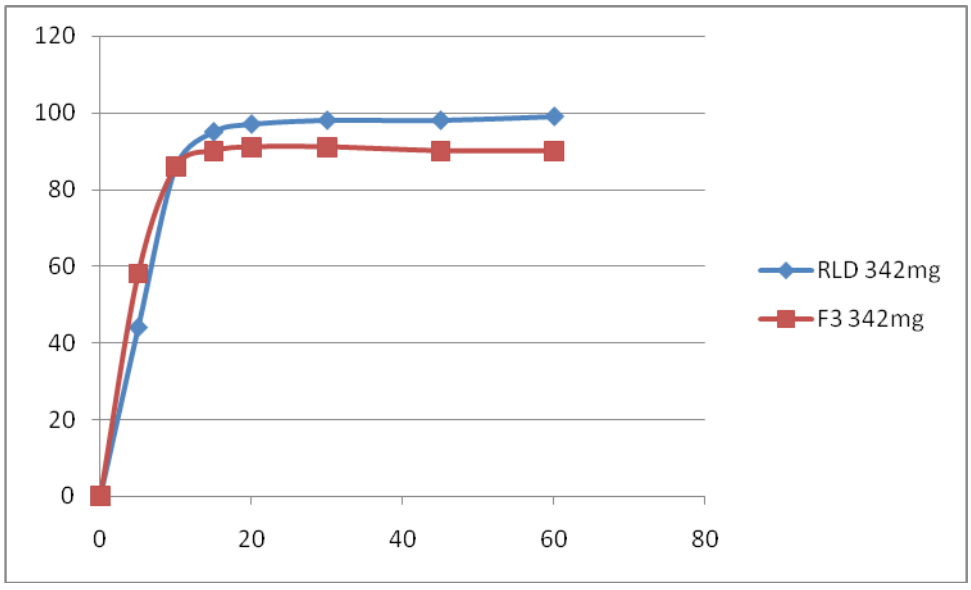


Figure No: 5 Dissolution graph of (F3) in pH 6.8 Buffer

Observation

Dissolution rate of trial F3 was found to be high when compared with the reference product.

Discussion

By increasing the disintegration time the release of drug in the initial time point can be controlled and hence it was decided to a trial, the drug release using the formula with the reduced disintegrants.

Formulation trial- F4

Table No: 23 Comparative Dissolution Profile of (F4) core tablet 342 mg in pH 6.8 Buffer

Type	USP Type - II (Paddle)		
RPM	50		
Temp 37ºC ± 0.5˚C			
Volume	900 ml		
Media	pH 6.8 Buffer		
Method:	HPLC		
S.No	**Time (minutes)**	**% Drug Release** **Reference product Tablet 342 mg**	**Formula F4 (core tablet 342 mg strength)**
1.	5	44	48
2.	10	86	82
3.	15	95	91
4.	20	97	93
5.	30	98	94
6.	45	98	95
7.	60	99	98
f1 value = 3.49 Dissimilarity factor & Similarity factor			
f2 value = 71.88			

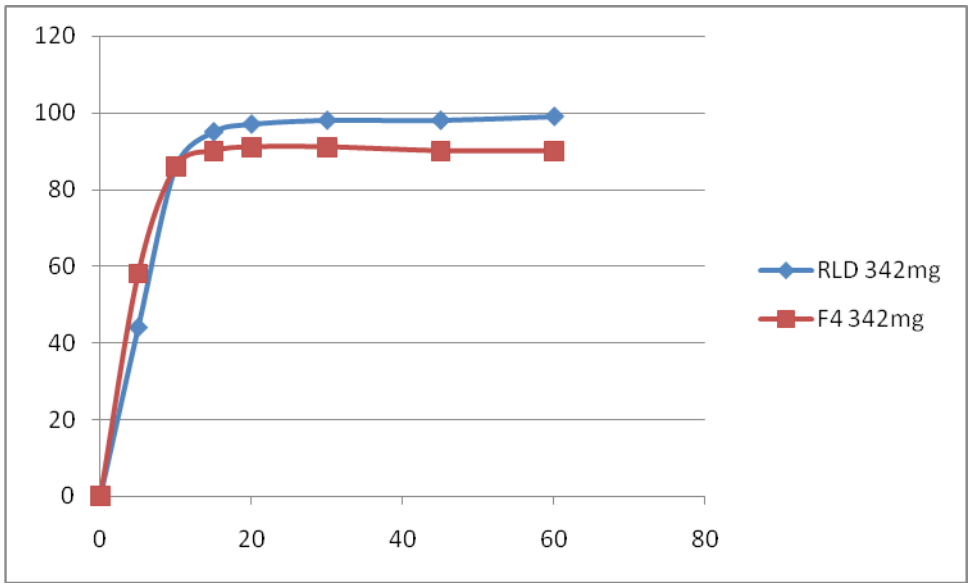


Figure No: 6 Dissolution graph of (F4) core tablet 342 mg strength in pH 6.8 Buffer

Discussion

The above results of drug release were found to be comparable with that of Reference product. It is also confirmed by the dissimilarity factor and similarity factor.

As the results are of core tablets was satisfactory, it was decided to coat the tablets and study the dissolution profile.

Table No: 24 Comparative Dissolution Profile of (F4) Film coated tablets 342 mg in pH 6.8 Buffer

Type	USP Type - II (Paddle)		
RPM	50		
Temp	37°C ± 0.5°C		
Volume	900 ml		
Media	pH 6.8 Buffer		
Method:	HPLC		
S.No	**Time (minutes)**	**% Drug Release**	
		Formula F4 (Film coated tablets 342 mg)	
1.	5	44	40
2.	10	86	81
3.	15	95	87
4.	20	97	91
5.	30	98	93
6.	45	98	94
7.	60	99	94
Dissimilarity factor & Similarity factor			
f1 value = 6.00		f2 value = 64.22	

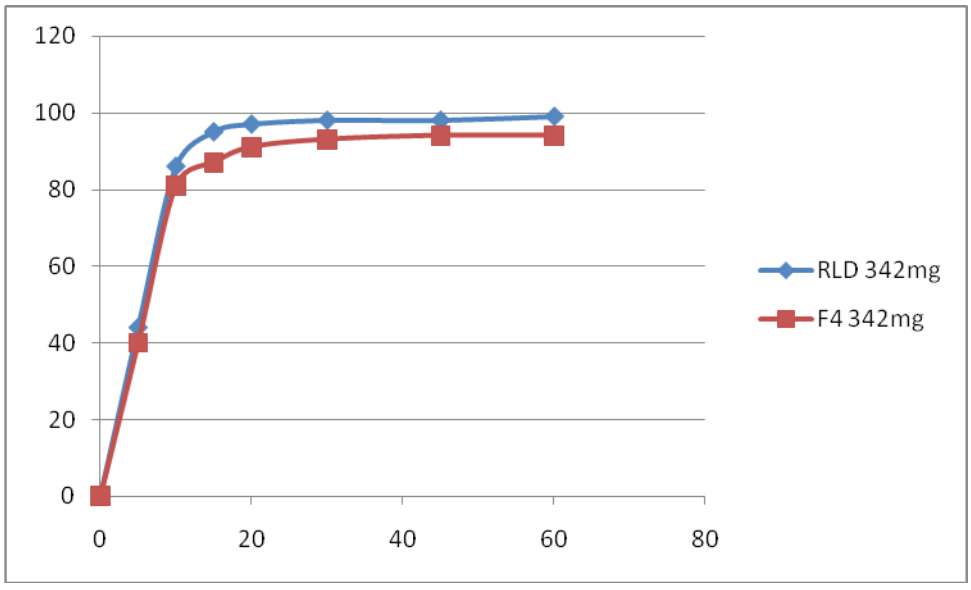


Figure No: 7 Dissolution graph of (F4) Film coated tablets 342 mg in pH 6.8 Buffer

Discussion

The dissolution profiling of coated tablets showed comparable with the Reference product. Based on the results of this trial, it was decided to take a reproducibility batch.

Formulation trial- F5 (Reproducibility batch)

Table No: 25 Comparative Dissolution Profile of (F5) Film coated tablets 342 mg in pH 6.8 Buffer

Type	USP Type - II (Paddle)		
RPM	50		
Temp	37°C ± 0.5˚C		
Volume	900 ml		
Media	pH 6.8 Buffer		
S.NoHPLC Method:	**Time (minutes)**		
% Drug Release		**Reference product Tablets 25mg**	
		44	40
2.	10	86	84
3.	15	95	99
4.	20	97	100
5.	30	98	101
6.	45	98	101
7.	60	99	101
Dissimilarity factor & Similarity factor			
f1 value = 3.40			
f2 value = 75.00			

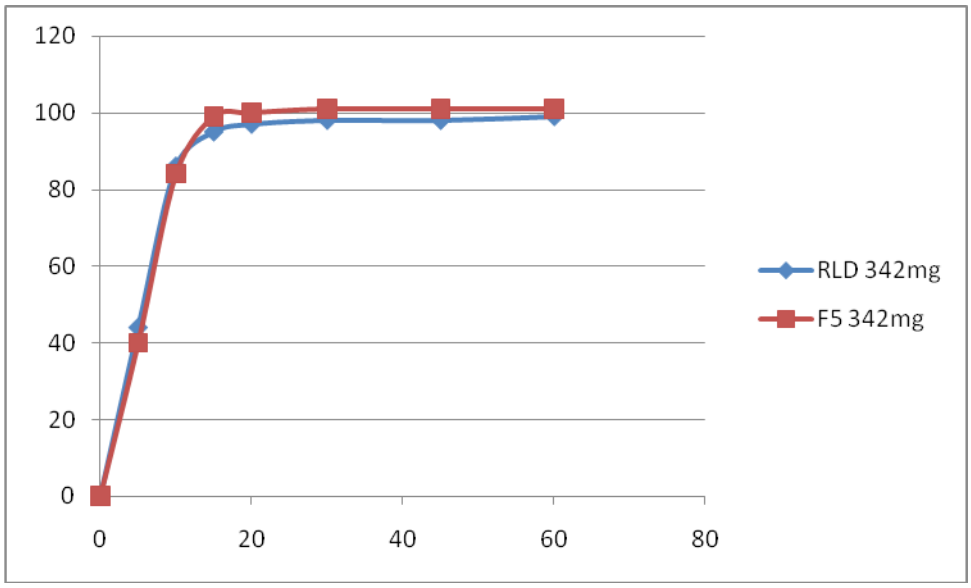


Figure No: 8 Dissolution graph of (F5) in pH 6.8 Buffer

Observation

The reproducibility batch showed comparable dissolution profiling with the reference product.

Conclusion

From the above trial it was confirmed that Test and Reference product dissolution profile were similar as the **Formulation trial- F4.** Hence finally Scale batch was planned.

SCALE UP BATCH

Formulation trial- F6

The scale-up batch was performed for dissolution in all 3 media as follows

Table No: 26 Comparative Dissolution Profile of (F6) Film coated tablets 342 mg in Purified water

Type	USP Type - II (Paddle)		
RPM	50		
Temp 37°C ± 0.5°C			
Volume	900 ml		
Media	Purified water		
Method:	HPLC		
S.No	**Time (minutes)**	**% Drug Release**	
		Reference product Tablets 342mg	**Formula F6 (Film coated tablets 342 mg)**
1.	5	44	45
2.	10	86	84
3.	15	95	92
4.	20	97	94
5.	30	98	94
6.	45	98	95
7.	60	99	100
f1 value = 2.76 Dissimilarity factor & Similarity factor			
f2 value = 77.62			

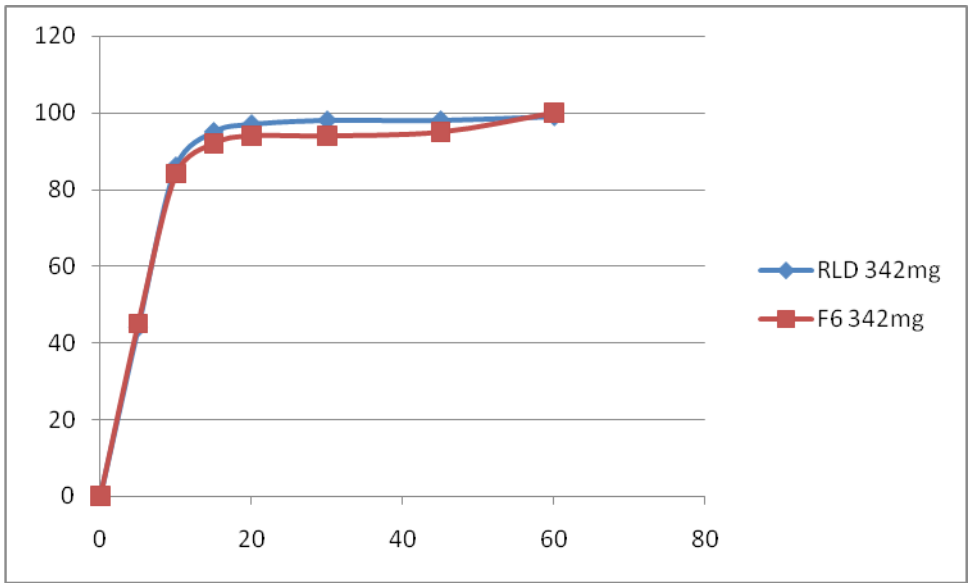


Figure No: 9 Dissolution graph of (F6) in Purified water

Table No: 28 Comparative Dissolution Profile of (F6) Film coated tablets 342 mg in 0.1N HCl

Type	USP Type - II (Paddle)		
RPM	50		
Temp 37°C ± 0.5°C			
Volume	900 ml		
Media	0.1N HCl		
Method:	HPLC		
S.No	**Time (minutes)**	**% Drug Release**	
		Reference product Tablets 342mg	**Formula F6 (Film coated tablets 342 mg)**
1.	5	26	28
2.	10	67	65
3.	15	90	90
4.	20	95	100
5.	30	96	101
6.	45	98	101
7.	60	98	101
Dissimilarity factor & Similarity factor			
f1 value = 3.51		f2 value = 74.00	

Figure No: 10 Dissolution graph of (F6) in 0.1N HCl

Table No: 28 Comparative Dissolution Profile of (F6) Film coated tablets 342 mg in pH 6.8 buffer

Type	USP Type - II (Paddle)		
RPM	50		
Temp 37ºC ± 0.5˚C			
Volume	900 ml		
Media	pH 6.8 Buffer		
Method:	HPLC		
S.No	**Time (minutes)**	**% Drug Release**	
		Reference product Tablets 342mg	**Formula F6 (Film coated tablets 342 mg)**
1.	5	40	47
2.	10	82	89
3.	15	96	97
4.	20	99	99
5.	30	100	100
6.	45	101	101
7.	60	102	102
f1 value = 1.38 Dissimilarity factor & Similarity factor			
f2 value = 75.75			

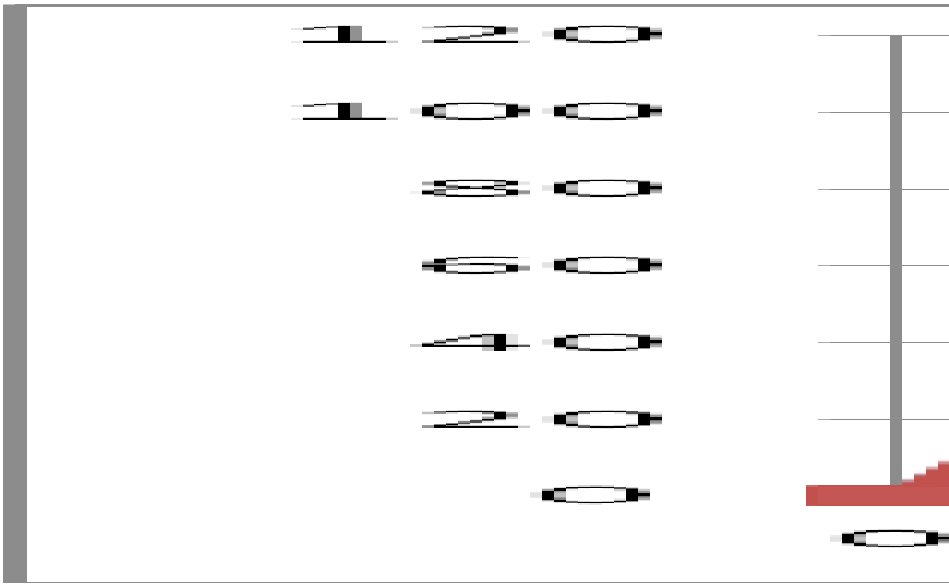


Figure No: 11 Dissolution graph of (F6) in pH 6.8 buffer

Observation

The dissolution profile of Test and Reference product was found to be similar. Also more than 85 % of the drug is released at 15 minutes, in all the 3 media (Purified water, 0.1 N HCl, pH 4.5buffer).

Discussion

The release profile was found to be satisfactory and comparable with that of Reference product. This is also confirmed by dissimilarity factor and similarity factor in all the dissolution media. Hence it was decided to pack the tablets in the proposed packaging and charge for stability.

Packing profile

The coated tablets were packed in PVC/PVDC blisters and loaded for stability.

Ibuprofen lysine 684mg strength:

Table No: 29 Characteristics of the Formulation trial – F8, F9, F10 & F11 blend

S.No	PARAMETERS	F7	F8	F9 (Reproducibility batch)	F10 (Scale up Batch)
1.	Bulk density (g/ml)	0.47	0.46	0.47	0.48
2.	Tapped density (g/ml)	0.59	0.57	0.57	0.57
3.	Carr's index (%)	20.34	19.29	17.54	15.78
4.	Hausner's ratio	1.26	1.23	1.21	1.18
5.	Flow property	Passable	Fair	Fair	Good
PARTICLE SIZE DISTRIBUTION					
	Sieve Analysis	**Cumulative % of drug release**			
		F7	**F8**	**F9**	**F10**
1.	# 40 mesh retention	30.00	28.00	27.00	27.00
2.	# 60 mesh retention	55.00	43.00	44.00	45.00
3.	# 80 mesh retention	68.00	56.00	58.00	58.00
4.	# 100 mesh retention	79.00	74.00	75.00	74.00
5.	# PAN	100.00	100.00	100.00	100.00

Among the formulation trials , F7 trial were found to be slightly coarser in nature. The remaining trials showed comparative reproducibility.

CORE TABLETS					
S.No	**PARAMETERS**	**F7**	**F8**	**F9 Finalized batch**	**F10 Scale up batch**
1.	Average Weight (mg)	792.33	790.88	791.56	791.33
2.	Thickness (mm)	5.50	5.57	5.62	5.59
3.	Hardness (N)	162	169	171	168
4.	Friability (% w/w)	0.07	0.02	0.03	0.02
5.	Disintegration Time (min & sec)	8mins 01 sec- 8mins 43 sec	9mins 47 sec- 9mins 58 sec	8mins 57sec- 9mins 01 sec	8mins 47 sec- 9mins 23sec
COATED TABLETS					
10	Thickness(mm)	6.1	6.48	6.54	6.51
12.	Disintegration time (min & sec)	8 mins 50 sec- 9 mins 02 sec	9mins 55sec- 10 mins 03sec	9mins 04sec- 9mins 34 sec	9mins 16 sec- 10mins 3sec

Table No: 29 Parameters of the Formulation trial – F7, F8, F9 & F10

DISSOLUTION PROFILES OF DOSE PROPORTIONAL STRENGTHS

Formulation trial – F7

Table No: 30 Dissolution profiles of (F7) in pH 6.8 buffer

Type	USP Type - II (Paddle)	
RPM	50	
Temp 37ºC ± 0.5˚C		
Volume	900 ml	
Media	6.8 buffer	
Method:	HPLC	
	% Drug release in pH 6.8 buffer	
Time in minutes	**Reference product**	**Formulation trial – F7 (Core tablet)**
	684mg	**684mg**
5	27	30
10	72	61
15	90	81
20	95	86
30	97	93
45	96	94
60	98	96
Dissimilarity factor & Similarity factor		
684 mg f1 value	6.75	
f2 value	57.07	

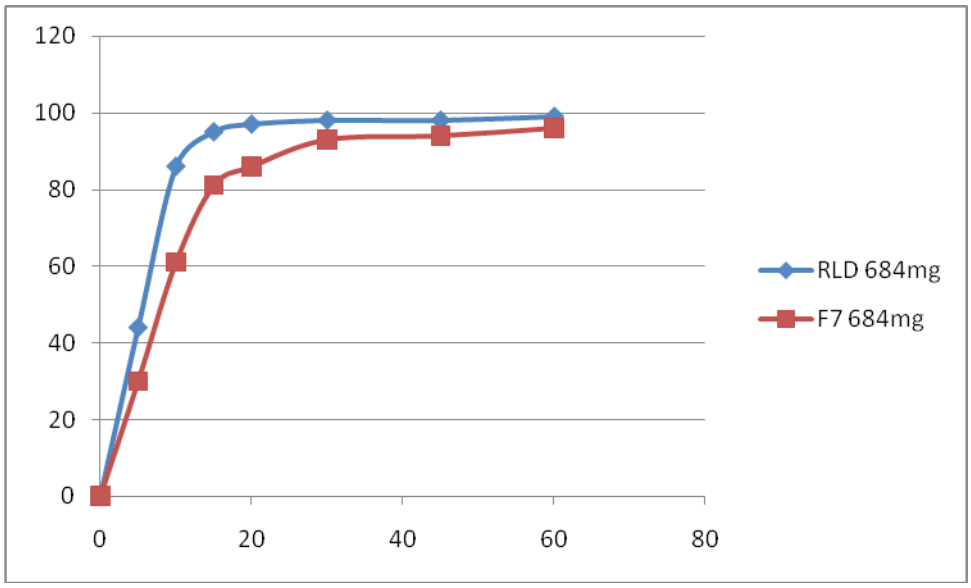


Figure No: 12 Dissolution graph for (F7) Core tablet in pH 6.8 buffer

Observation

Dissolution rate of trial F7 was found to be lesser when compared with the reference product.

Disscussion

The drug release of this feasibility trial made and found releases less than the reference product. so ,the next trail is do with change in the concentration of Sodium starch glycolate and Povidone.

Formulation trial– F8

Table No: 31 Dissolution profiles of (F8) in pH 6.8 buffer

Type	USP Type - II (Paddle)	
RPM	50	
Temp 37°C ± 0.5°C		
Volume	900 ml	
Media	6.8 buffer	
Method:	HPLC	
	% Drug release in pH 6.8 buffer	
Time in minutes	**Reference product**	**Formulation trial – F8**
	684mg	**684mg**
5	27	29
10	72	65
15	90	86
20	95	89
30	97	92
45	96	95
60	98	96
Dissimilarity factor & Similarity factor		
684mgf1 value	4.70	
f2 value	67.63	

Figure No: 13 Dissolution graph for (F8) in pH 6.8 buffer

Observation

The dissolution profile of all the dose proportionate strengths of formulation F-8 was comparable with the reference product. Also more than 85% of drug released at 15 minute time points like reference product.

Disscussion

The dissolution profile of this batch was found to be satisfactory; hence a reproducibility batch was planned and executed using the same formula and process of this batch.

Formulation trial – F9

Table No: 32 Dissolution profiles of (F9) in pH 6.8 buffer

Type	USP Type - II (Paddle)	
RPM	50	
Temp 37°C ± 0.5°C		
Volume	900 ml	
Media	6.8 buffer	
Method:	HPLC	
	% Drug release in pH 6.8 buffer	
Time in minutes	**Reference product**	**Formulation trial – F9**
	400mg	**400mg**
5	27	29
10	72	66
15	90	86
20	95	90
30	97	93
45	96	95
60	98	97
Dissimilarity factor & Similarity factor		
f1 value	4.0	
f2 value	70.60	

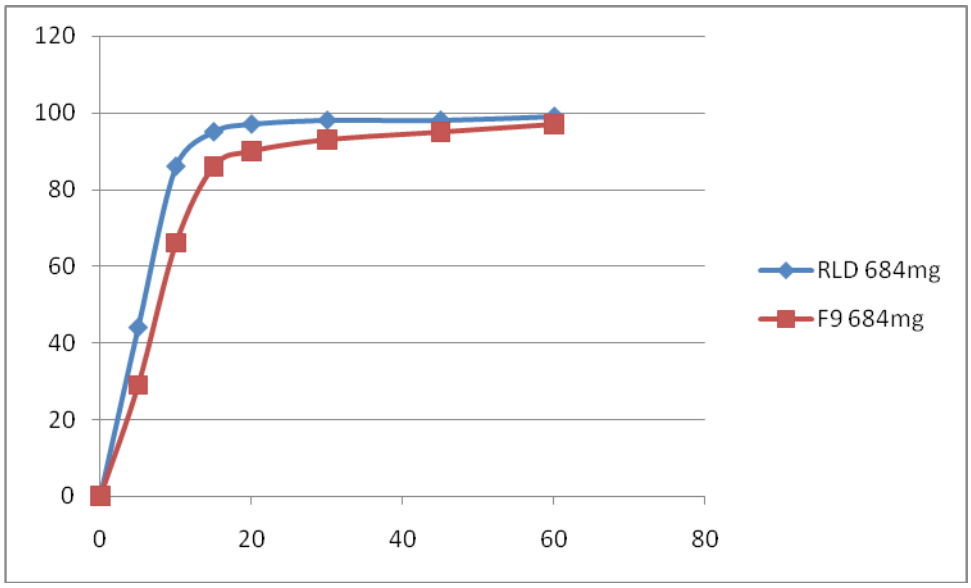


Figure No: 14 Dissolution graph for (F9) in pH 6.8 buffer.

Observation

The results indicate that the dissolution profile of the two dose proportionate strengths of the formulation trialF-9 was comparable and reproducible as the formulation trial F-8.

Discussion

Hence it was planned to formulate a scale up batch and to charge it for stability study.

SCALE UP BATCH

Formulation trial – F10

Table No: 33 Dissolution profiles of (F10) in Purified water

Type	USP Type - II (Paddle)	
RPM	50	
Temp	37°C ± 0.5˚C	
Media900 ml Volume	Purified water	
Method:	HPLC	
	% Drug release in Purified water	
Time in minutes	**Reference product**	
Formulation trial – F10	**684mg**	**684mg**
	27	29
10	72	66
15	90	87
20	95	91
30	97	93
45	96	95
60	98	97
Dissimilarity factor & Similarity factor		
f1 value	3.65	
f2 value	72.39	

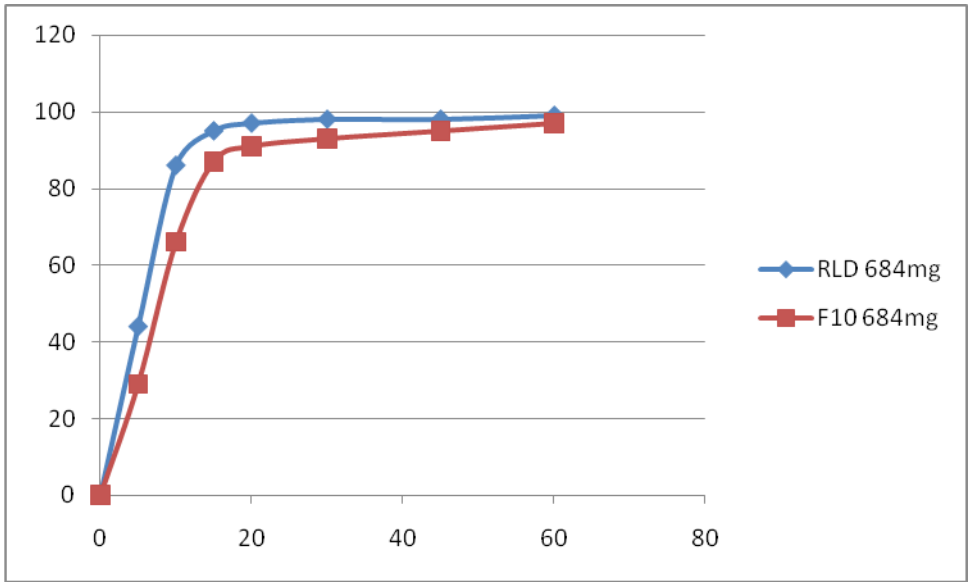


Figure No: 15 Dissolution graph for (F10) in Purified water

DISSOLUTION PROFILE IN 0.1N HCl

Table No: 34 Dissolution profiles of (F10) in 0.1N HCl

Type	USP Type - II (Paddle)	
RPM	50	
Temp	37°C ± 0.5°C	
Volume	900 ml	
Media	0.1N HCl	
Method:	HPLC	
	% Drug release in 0.1N HCl	
Time in minutes	**Reference product**	**Formulation trial – F10**
	400mg	**400mg**
5	27	30
10	72	66
15	89	86
20	94	91
30	96	93
45	98	97
60	98	98
Dissimilarity factor & Similarity factor		
f1 value	3.31	
f2 value	73.55	

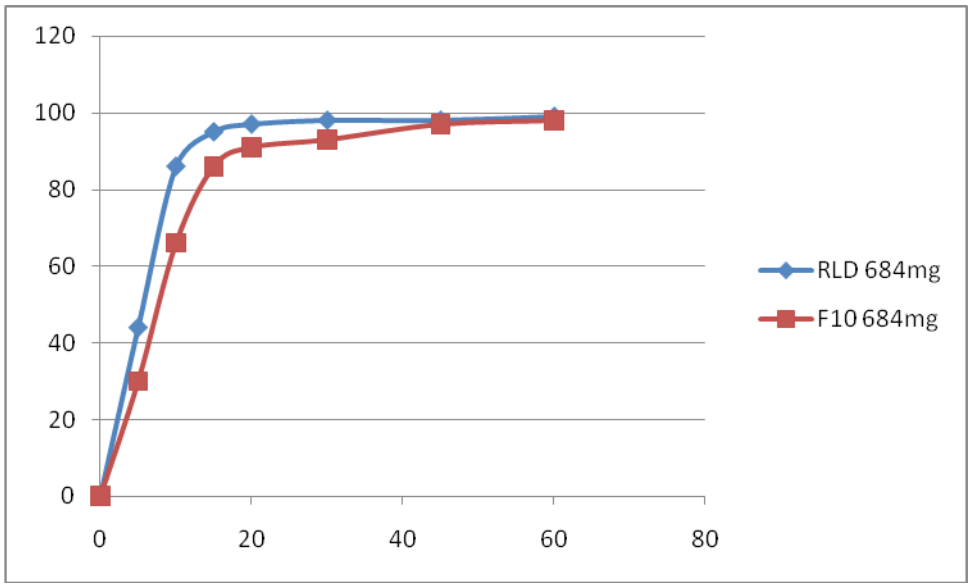


Figure No: 16 Dissolution graph for (F10) in 0.1NHCl

DISSOLUTION PROFILE IN pH4.5 BUFFER

Table No: 35 Dissolution profiles of (F10) in pH 6.8 Buffer

Type	USP Type - II (Paddle)
RPM	50

Temp	37ºC ± 0.5˚C	
Volume	900 ml	
Media	pH 6.8 Buffer	
Method:	HPLC	
Formulation trial – F10	**% Drug release in pH 6.8 Buffer**	
Reference product	**684mg**	**684mg**
Time in minutes	22	29
10	63	66
15	85	87
20	90	89
30	92	90
45	92	91
60	91	92
Dissimilarity factor & Similarity factor		
f1 value	3.18	
f2 value	74.25	

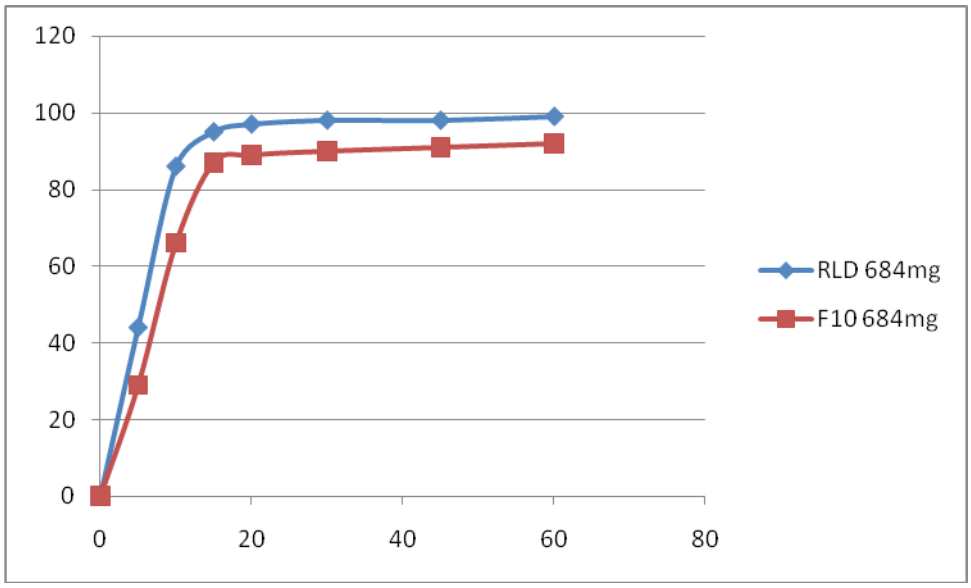


Figure No: 17 Dissolution graph for (F10) in pH 6.8 Buffer

Observation

The dissolution profile of the test and reference product was comparable which is confirmed by Dissimilarity factor and similarity factors. Also more than 85% of drug released at 15 minutes time points like reference products in all the 3 media (Purified water, 0.1 N HCl, purified water).

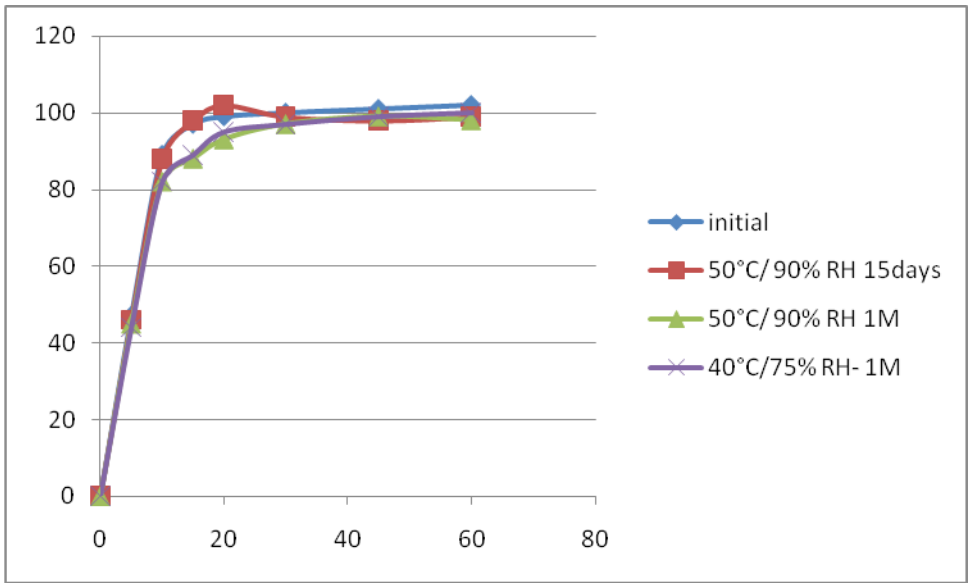
Discussion

As the dissolution profile in all the 3 media was found to be satisfactory, hence the tablets were packed in PVC/PVDC blisters and charged for stability study in both stress condition for 15 days &1month (50°C/90%RH) and 1, 2, 3 month's at accelerated condition (40°C/ 75%RH).

Table No: 36 Stability Studies of Ibuprufen lysine Tablets 342mg (Formulation trial-6)

Stability studies 50°C/90% & RH 40°C/75% RH -F6 scale up batch(342 mg)						
Parameters	**Initial**	**Results**				
Description	white in colour	white in colour				
		50°C/ 90% RH 15days	**50°C/ 90% RH 1M**	**40°C/75% RH- 1M**	**40°C/75% RH- 2 M**	**40°C/75% RH- 3 M**
Avg. wgt (mg)	403.56	404.01	403.98	402.89	401.99	403.45
Hardness(N)	143	142	146	145	143	144
Thickness(mm)	4.60	4.69	4.59	4.58	4.60	4.59
Disintegration time(min& sec)	7mins 31 sec-7mins 46sec	7mins 30sec-7mins 55sec	7mins 12sec-7mins 33 sec	7mins 03sec-7mins 40sec	7mins 27sec-7mins 51sec	7mins 01 sec- 7mins 34sec
DISSOLUTION						
Time (minutes)	**Initial**	**50°C/ 90% RH 15days**	**50°C/ 90% RH 1M**	**40°C/75% RH- 1M**	**40°C/75% RH- 2 M**	**40°C/75% RH- 3 M**
5	47	46	45	44	45	46
10	89	88	82	82	79	81
15	97	98	88	89	86	90
20	99	102	93	95	98	99
30	100	99	97	97	100	100
45	101	98	99	99	96	95
60	102	99	98	100	102	99
Assay	99-102%	99.33	98.87	99.84	100.03	101.00
Related substances by HPLC (%)						
Known impurity	NMT 0.2%	0.04	0.02	0.04	0.05	0.03
Unknown Impurity	NMT 0.15%	0.02	0.03	0.06	0.02	0.05
Total Impurity	NMT 1.0 %	0.08	0.07	0.11	0.09	0.09

Figure No: 18 Stability Studies graph of Ibuprufen lysine Tablets 342mg (Formulation trial-6)


120
100
80
60
40
20
0
0
20
40
60
80
initial
50°C/ 90% RH 15days
50°C/ 90% RH 1M
40°C/75% RH- 1M

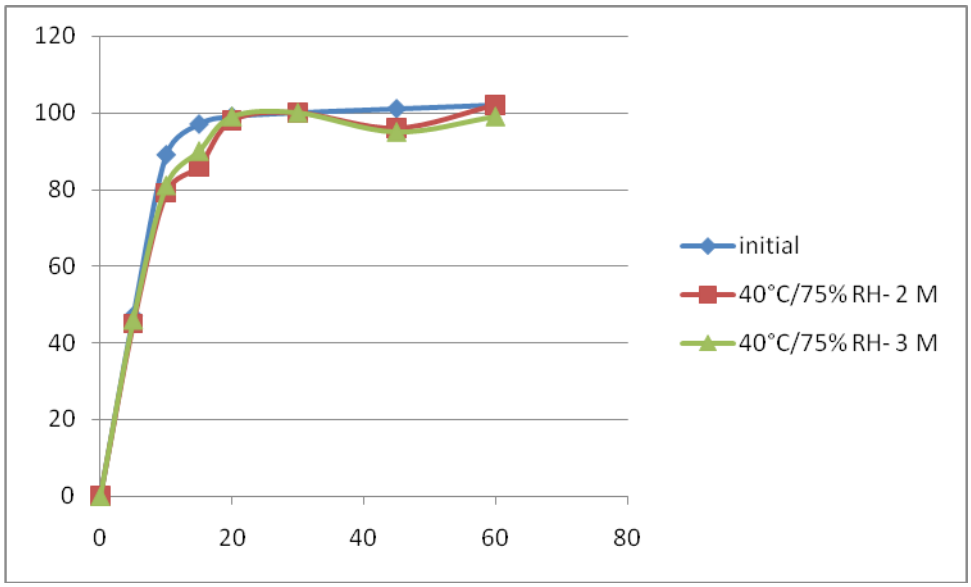

120
100
80
60
40
20
0
0
20
40
60
80
initial
40°C/75% RH- 2 M
40°C/75% RH- 3 M

Table No: 37 Stability Studies of Ibuprufen lysine Tablets 342mg (Formulation trial-10)

Stability studies 50°C/90% & RH 40°C/75% RH -F10 scale up batch(684 mg)						
Parameters	**Initial**	**Results**				
Description	Almost white in colour	Almost white in colour				
		50°C/ 90% RH 15days	**50°C/ 90% RH 1M**	**40°C/75% RH- 1M**	**40°C/75% RH- 2 M**	**40°C/75% RH- 3 M**
Avg. wgt (mg)	817.65	818.54	816.5	817.6	818.02	817.25
Hardness(N)	189	188	190	189	189	190
Thickness(mm)	6.51	6.47	6.52	6.51	6.49	6.47
Disintegration time(min& sec)	9mins 16 sec-10mins 3sec	9mins 08 sec- 9mins 56sec	9mins 17sec-10mins 01sec	9mins 21 sec- 10mins 02 sec	9mins 45sec-10mins 04 sec	9mins 15sec-10mins 05sec
Dissolution						
Time (minutes)	**Initial**	**50°C/ 90% RH 15days**	**50°C/ 90% RH 1M**	**40°C/75% RH- 1M**	**40°C/75% RH- 2 M**	**40°C/75% RH- 3 M**
5	29	30	28	29	28	29
10	66	59	65	65	64	66
15	87	85	87	87	88	89
20	91	92	92	91	90	93
30	93	95	94	93	94	95
45	95	94	95	95	96	97
60	97	98	97	97	98	99
Assay	99-104%	99	101	102	99	103
Related substances by HPLC (%)						
Known impurity	NMT 0.2%	0.03	0.02	0.04	0.04	0.03
Unknown Impurity	NMT 0.15%	0.02	0.02	0.03	0.03	0.02
Total Impurity	NMT 1.0 %	0.08	0.07	0.11	0.09	0.09

Observation and Discussion:

All the results were found to be satisfactory and within the specified limit. There were no significant changes after the 1 month, 2 months and 3 months study, further the stability studies

will be performed and will be evaluated for the confirmation to achieve the specifications of the reference product.

7. CONCLUSION

The Dissertation work entitled, "Formulation Development and Evaluation of NSAID's tablets" was carried out for the optimization of the formulation to meet the quality standards with regards to API, excipients, manufacturing process and finished product.

Drug-excipient compatibility studies were carried out and the results showed that there was no physical and chemical change in the API. This indicated that, the drug was compatible with the formulation components. Povidone k30, sodium starch glycollate and magnesium stearate were selected as inactive excipients for the lab scale development.

The Prototype formulations were developed (F1-F10) and the formulation trial-F6 of 342 mg strength and the formulation trial-F10 of 684 mg strength the invitro drug release profile was optimized to the Innovator product and it is subjected to further studies.

The finalized batch, Confirmatory and scale up formulation's was taken for stability studies as per the ICH Guidelines, all batch were packed in HDPE container and charged at 50°C/ 90% RH for the period of 15 days & 1M and 40°C/75% RH for the period of 1M, 2M and 3M. The results were found satisfactory and it complies the satisfactions.

SUMMARY

Among the various routes of drug delivery system, Oral route is the oldest and most common route of drug administration. In oral administration, tablet is one of the most preferred dosage forms because of its ease of manufacturing, convenience in administration, accurate dosing and higher stability compared with oral liquids.

The project work entitled "Formulation Development and Evaluation of Anti inflammatory drug as Immediate Release Tablets" was carried out in the study. The study was mainly focused on the optimization of the formulation to meet the reference product characteristics, based on the excipients of reference product, the excipients were selected for Drug Excipient compatibility study trials. The binary mixtures were filled in vials and closed with bromo butyl rubber stoppers & crimped with tear off clear lacquer aluminum seals and charged at 50°C/90% RH and 40°C/75% RH conditions. All the excipients used in the Drug-Excipients compatibility study were found to be compatible with API.

The development was started by using direct compression technique In formulation trial-F3 (342 mg) was found that the drug release was more about 20% on comparing the reference product, at initial time point(5^{th} minute). Hence a next formulation trial-F4 was planned to reduce the drug release. The formulation trial-F4 was formulated using sodium starch glycolate. This gave satisfactory and comparable dissolution profile with reference product (Reference Products). Hence a reproducibility batch (formulation trial-F5) followed by scale-up batch (formulation trial-F6) was formulated.

The scale-up batch (formulation trial-F6) dissolution results in other media was also found to be comparable and more than 85% of drug released at 15 minute time points like reference product.

Further the 684 mg strength started in by direct compression technique method was adopted (formulation trial-F7).The drug release profile of all the dose proportionate strength (formulation trial-F7) was found to be similar, but found to release less than 85% of drug at 15 minutes on comparing the reference products. Hence the next formulation trial (formulation trial-F8) was formulated with povidone k30 and sodium starch glycolate concentration to reduce the drug release at the initial time points.

The formulation trial-F8 gave a satisfactory dissolution results with more than 85% of drug release at 15 minute time points and a comparable drug release profile on comparing the reference products. Based on this trial, a reproducibility batch (formulation trial-F9) and a scale-up batch (formulation trial-F10) was formulated which showed a satisfactory and similar drug release profile as that of formulation trial-F8. The finalized formulations evaluated for physical characteristics and chemical characteristics were found to be satisfactory and comparable with the reference products.

The formulation trial-F6 of 342 mg strength and the formulation trial-F10 of 684 mg strength was taken for stability studies as per the ICH Guidelines, all batch were packed in PVC/PVDC blisters and charged at 50°C/ 90% RH for the period of 15 days & 1M and 40°C/75% RH for the period of 1M, 2M and 3M.

The 15 days and 1 month stability data at stressed condition showed no characteristic changes when compared to the initial results which indicate the product is stable. The 1 month, 2 month and 3 month stability at accelerated condition was also found to be within the specified limits.

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